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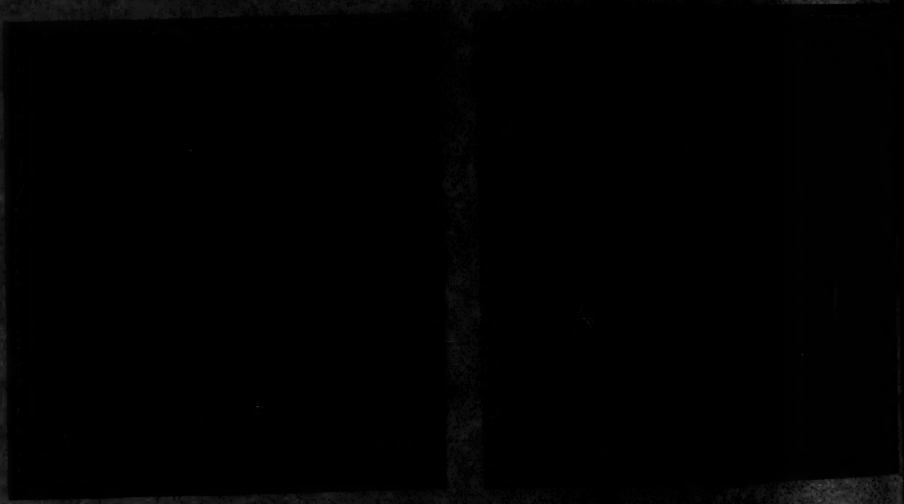

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PATHOGENESIS OF CONCURRENT EYE AND JOINT DISEASES*

BY

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THE reasons for discussing the subject of concurrent eye and joint diseases in this Society are (*a*) the great interest displayed in it by Swedish clinicians (Sjögren, Stenstam, Stig Holm, Edström and Osterlind); and (*b*) the recent advances concerning the physiopathology and serological diagnoses of the joint diseases (blood cultivation and antibody measurements, including the antistreptolysin titre and agglutination test). These advances, together with the intensified research work within the field of allergy, which has led to the discovery of the antihistamine substances, as well as to the unfolding of further possibilities in virus pathology (thanks to the electron microscope and better methods of cultivation) have thrown new light on various joint diseases. As the aetiology and

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pathogenesis of many cases of iridocyclitis, scleritis and phlyctenular conjunctivitis are still obscure, and as these diseases are very frequently met with in association with joint diseases, it might be of interest to analyse the nature and frequency of eye symptoms in joint diseases in order thus to attempt to elucidate the pathogenic conditions.

The clinical pictures of concurrent eye and joint diseases have been described both in synoptic form and on the basis of original materials (Franceschetti, 1946; Sorsby and Gormaz, 1946; Edström, 1937), but aetiological and pathogenic outlines have not been drawn.

The incidence and symptomatology of concurrent eye and joint diseases will first be recapitulated in brief, the main stress being laid on the features relevant to the present investigation.

The medical (" rheumatic") joint diseases complicated by eye symptoms (Table I) comprise 2 groups: acute diseases (rheumatic fever, gonorrhoeal arthritis, and simple, urethritic polyarthritis or Reiter's disease) and chronic diseases (primary chronic polyarthritis, Still's disease, and ankylopoietic spondylo-arthritis or Pierre Marie-Strümpell-Bechterew's disease). Uratic arthritis is —with some reservation—included among the acute diseases.

TABLE I

Incidence (per cent.) of eye symptoms complicating joint diseases

	Conjunctivitis	Iritis	Sicca-syndrome
Acute joint diseases			
Rheumatic fever	5–10	4–5	—
Gonorrhoeal arthritis	10	5	—
Reiter's disease	80	10	—
Uratic arthritis	—	2	—
Chronic joint diseases			
Primary progressive chronic polyarthritis	—	2–5	10
Still's disease...	—	20	—
Ankylopoietic spondylo-arthritis ... (Bechterew-Strümpell-Marie)	—	15–50	—

In Denmark the most frequent form of joint disease is rheumatic fever with about 4,000 fresh cases annually. Next in frequency follows primary chronic polyarthritis with 3-400 fresh cases annually and a total of about 8,000 cases. All the other joint diseases are far less frequent. Gonorrhoeal arthritis is a rare phenomenon since the introduction of sulphonamide and penicillin treatment. Before the era of chemotherapy 1 to 5 per cent. of the gonorrhoea cases were complicated by joint diseases (Heerfordt, in 1909, collected 191 joint cases among 2,300 patients with gonorrhoea). The triad of polyarthritis, non-specific urethritis, and conjunctivitis (Reiter, 1916) has been observed with increasing frequency in many countries during and after the second world war (Skydsgaard, Haar, Paronen, whose material is the largest so far) and may be found also in women (Zewi found 6 women among 10 cases in 1947). In Paronen's abundant Finnish material (1948), comprising 325 cases of Reiter's disease, the syndrome was complete in 70 per cent., while joint symptoms were present in 98 per cent., eye symptoms in 90 per cent., and urethritis in 79 per cent. Initial dysentery-like gastro-enteric symptoms were found in 96 per cent.

Still's disease (1897) is a variety of chronic polyarthritis (periarthritis) affecting children, chiefly girls. In addition to chronic iridocyclitis, often with zonular keratitis, the disease is associated with polyadenitis and enlargement of the spleen, and the general condition is affected (Friedländer, Ejler Holm, Blegvad, Poulsen).

Uratic arthritis and ankylopoietic spondylitis being also fairly rare, the joint diseases of the most immediate importance in this connexion are rheumatic fever, primary chronic polyarthritis, and Reiter's disease.

All the above joint diseases, except uratic arthritis, may be included under the heading of infective arthritis. The arthrosis group, on the other hand, is not associated with eye symptoms. The articular symptomatology is characterized by being polyarticular. Ankylopoietic spondylitis begins in the sacro-iliac joints, whence it proceeds up through the joints of the vertebral column.

The eye symptoms in these joint diseases comprise in the main three distinct groups: (1) endogenous conjunctivitis, including episcleritis and scleritis, (2) iritis and iridocyclitis, and (3) the sicca-syndrome. In rare cases may be added optic neuritis and ocular palsies.

Iritis may be found in association with any one of the above seven joint diseases, at frequencies varying from 2 to 50 per cent. It is most rare in association with uratic arthritis (2 per cent.), primary chronic polyarthritis (2 to 5 per cent.), gonorrhoeal

arthritis and rheumatic fever (4 to 5 per cent.), but more frequent in Reiter's disease (10 per cent.) and ankylopoietic spondylitis (15 to 50 per cent.) (Comroe, Heerfordt, Paronen). The nature of the iritis in the acute joint diseases is chiefly acute, serous, with no essential characteristic, and in the chronic diseases chiefly chronic, though with acute exacerbations. In ankylopoietic spondylitis there is found an abundant exudation of fibrin into the anterior chamber. Still's disease may be associated with zonular keratitis.

Conjunctivitis occurs as a characteristic symptom only in the acute joint diseases, ranging in frequency from 10 to 80 per cent. (80 per cent. in Reiter's disease, 10 per cent. in gonorrhoeal arthritis, and 5 to 10 per cent. in rheumatic fever). Clinically it may have the form of a more or less superficial phlyctenular conjunctivitis or episcleritis (Heerfordt's subconjunctivitis epibulbaris) or a more diffuse bilateral conjunctivitis with limited secretion.

The sicca-syndrome (Sjögren's disease) is a characteristic occurrence only in primary chronic polyarthritis, with a frequency of 10 per cent. (Stenstam and Stig Holm, 1947). The clinical picture, described in detail by Sjögren (1933-40) and placed in relation to Plummer-Vinson's syndrome and ariboflavinosis (Godtfredsen, 1947) will not be discussed further. It should be remembered, however, that the disease is a generalized systemic affection of the secretory structures in the upper respiratory and alimentary tracts, lacrimal glands, pancreas and vaginal glands, with humoral changes (hyperglobulinaemia). The symptomatology is characterized by keratoconjunctivitis sicca, xerostomia, atrophic rhinitis, histamine-refractory achylia and desquamatory colpitis.

Even though from 2 to 50 per cent. of the joint diseases mentioned here are complicated by different eye symptoms, the total number of cases is rather limited, because the frequently occurring joint diseases most rarely show eye complications, whereas the reverse is the case for the rarer joint diseases (ankylopoietic spondylitis, Still's disease, and Reiter's disease). However, in the Eye Department of the Municipal Hospital, Copenhagen, we recently found that by systematic fractional urine examination (" two- or three-tube test ") with inspection for fibres in all iritis cases we may discover a number of otherwise overlooked cases of Reiter's disease. Likewise the ophthalmologists will no doubt diagnose a greater number of ankylopoietic spondylitis cases by bearing this disease in mind when seeing iritis patients who have difficulty in pushing the chin forwards to the chin support of the slit-lamp, owing to the reduced mobility of the cervical part of the vertebral column.

PATHOGENESIS

The pathogenesis of the joint diseases mentioned in the present paper, is by no means fully elucidated, and there is no agreement in the literature. The most current views (Comroe, Cecil) are those summarised below.

Rheumatic fever is presumably an allergo-toxic reaction to infection with haemolytic streptococci, a hypothesis that is supported by the antistreptolysin titre, which is increased in 80 per cent. of the cases (> 200) (Kalbak; Winblad). In gonorrhoeal arthritis there is found gonococcaemia, and cultivation of gonoccoci from synovial fluid was performed before the gono-complement fixation reaction became positive. Reiter's disease, which originally was supposed to be due to a spirochaete, is still aetiologically obscure. The most recent literature ventilates the possibility of a virus, which, however, it has not yet been possible to cultivate. Reiter's disease often has an initial gastro-enteric stage, after which the characteristic triad manifests itself, probably released by an allergo-toxic agent. In uratic arthritis the essential feature is the pathological purine metabolism with increased serum uric acid values, and thus the pathogenesis differs from those of the other joint diseases. As for the three chronic joint diseases the aetiology is unknown, but is presumably infective and possibly—like Reiter's disease—of a virus nature with an allergo-toxic pathogenesis. Constitutional, possibly endocrine factors, are likely to play a part (Lövgren, 1945). This may explain the pronounced sex difference: primary chronic polyarthritis and Still's disease are most frequent among women, whereas Reiter's disease and ankylopoietic spondylitis are most frequent among men (Paronen; Sorsby and Gormaz).

In primary chronic polyarthritis 10 per cent. of the cases have increased antistreptolysin titre, which is only slightly above the normal findings (6 per cent., Kalbak). The agglutination test for haemolytic streptococci, on the other hand, yields increased values in 80 per cent. (Kalbak, 1946), a finding which has supported the theory of the aetiological importance of haemolytic streptococci. However, the most recent investigations (Wallis, 1947) seem to show that the agglutination reaction is not specific, but a more general indication of an abnormal serum instability (similar to the conditions which may give a positive Takata reaction). The agglutination test gives a negative reaction in ankylopoietic spondylitis.

Common to the above joint diseases—except uratic arthritis—is thus the fact that the pathogenesis seems to be an allergo-toxic reaction to a primary infectious agent, the aetiology of which is

clear for rheumatic fever (haemolytic streptococci) and gonorrhoeal arthritis. The aetiology of the other joint diseases is obscure; the possibility of a virus infection is present.

The clinical picture and the course of these joint diseases with and without associated eye signs being otherwise alike (Stenstam; Holm) we may suppose that the pathogenesis of the eye signs is the same as that of the joint symptoms, being thus of an allergo-toxic nature. This hypothesis is supported by the clinical picture of the eye symptoms. Phlyctenular conjunctivitis, or episcleritis, corresponds exactly to the eye signs in well-known allergic conditions, such as serum disease, sulphonamide allergy and tuberculin allergy. The histopathological picture of the phlyctenules is the same in these diseases, presenting an aggregation of polymorphonuclear leucocytes, small lymphocytes, and epithelioid cells, sometimes polynuclear, reminiscent in structure of Aschoff's nodules in the myocardium and the rheumatic nodules in the skin demonstrated in rheumatic infection (Edström and Osterlind). The iritis attending the joint disease resembles the monosymptomatic primary iritis, the aetiology of which is to an increasing extent believed to be allergo-toxic (Duke-Elder, 1947). Bjorn Foss' experimental work on anaphylactic iritis (1947) tends in the same direction. The pathogenesis of the sicca-syndrome may vary. Both hormone-biological factors and avitaminosis may play a part; but in the great majority of the sicca cases associated with primary chronic polyarthritis, the infective pathogenesis with an allergo-toxic reaction is the most likely one.

DISCUSSION

That the eye may be affected in the joint diseases mentioned above is probably due to various factors, of which a few will be pointed out. It has been shown that the blood-synovial barrier of the joints and the blood-aqueous barrier of the eye exhibit the same conditions of permeability for the substances involved in the inflammatory processes. In experimental streptococcaemia in animals (Angevine and Rothbard, 1940) the ciliary processes of the eye and the synovia of the joints were the places where the streptococci by preference elicited inflammatory changes.

Human clinical medicine does not, however, bear out the animal experimental findings. Thus among 72 cases of streptococcaemia, Sylvest (1946) found 6 with eye signs (iritis, vitreous body abscess, and conjunctivitis), but without joint symptoms, which were present in one-third of the remaining cases.

The primary infective agent is unknown in several of the concurrent eye and joint diseases reported in this paper, but

known in gonorrhoeal arthritis, and is presumably haemolytic streptococci in rheumatic fever (where 80 per cent. had increased streptolysin-titre). For primary acute iritis without joint symptoms, on the other hand, the significance of haemolytic streptococci is doubtful since the antistreptolysin titre does not here differ from the normal (Björk, 1947).

The supposed allergo-toxic processes resulting in concurrent eye and joint diseases seem to bear no relation to allergic constitution and heredity, since these patients do not to any conspicuous extent present otherwise well-known allergic symptoms, such as vasomotor rhinitis, hay fever and urticaria.

It should be pointed out that many of the above concurrent eye and joint diseases have a more generalized character, presenting signs in other organs or systems as well, *e.g.*, the cardiac complications in rheumatic fever, the generalized glandular affection in Sjögren's syndrome, the polyadenitis and the splenic enlargement in Still's disease, the urethritis in Reiter's disease, etc. This generalized symptomatology has clinico-topographic points of resemblance to various characteristic diseases where not only the eyes and the joints are affected, but also the skin and the mucous membranes around the orifices of the body—the so-called pluri-orificial location (with conjunctivitis, stomatitis, affection of the external genitalia, *e.g.*, balanitis, vulvo-vaginitis)—and where the pathogenesis is supposed to be allergo-toxic on an infective basis.

The most important diseases with cardinal signs constituting a more or less constant tetrad of signs from eyes, joints, skin, and oral and genital mucous membranes have been set out in Table II, grouped according to the supposed aetiology (bacteria, virus, unknown, intoxication). The frequently protean clinical pictures will not be discussed in detail, but brief mention may be made of the following facts. Stevens-Johnson's syndrome (1922) is a special form of manifestation of exudative erythema multiforme* with concurrent skin exanthema of cockade-like eruptions increasing to bullous dermatitis, as well as stomatitis, conjunctivitis, and balanitis, more rarely polyarthritis (Edmund; Jersild; Ustvedt, 1948). A similar clinical picture is met with in the exceedingly rare Behcet's syndrome (Tage Jensen, Bechgaard), where, however, the skin lesion may be more of the character of erythema nodosum. Furthermore there is found a recurrent iritis with hypopyon, aphthous stomatitis, and genital affection. Analogous pictures are seen when foot-and-mouth disease affects humans (Bojlén). Acute disseminated erythematous lupus is likewise a rare and severe disease (V. Mortensen; Cordes

* Recently discussed by J. E. Wolff (1949) in *Brit. J. of Ophthal.*, **33**, 110.

TABLE II

Diseases with concurrent symptoms from eyes, joints, skin and mucous membranes

	Eyes	Joints	Skin	Mucous membranes (stomatitis, balanitis)
Virus diseases or obscure aetiology				
Reiter's disease	+	+	+	+
Stevens-Johnson syndrome ...	+	(+)	+	+
Behcet's syndrome	+	(+)	+	+
Foot-and-mouth disease	+	?	+	+
Acute disseminated erythematous lupus	+	+	+	+
Measles, chicken-pox	+	(+)	+	+
Bacterial diseases				
Gonococcal sepsis	+	+	(+)	+
Streptococcal sepsis	(+)	+	+	+
Intoxications				
Sanocrysin, arsenicals	+	(+)	+	+
Serum sickness	+	+	+	+

(+) means less significant.

and Aiken, 1947) with a polymorphous picture comprising the skin lesion, polyarthritis, lymphadenitis, endocarditis and pluri-orificial ulcerative mucosal affections.

Gonococcaemia and streptococcaemia have already been mentioned. The morphology of the exanthemata may here vary a great deal. Intoxications by heavy metallic salts, notably sanocrysin (*cf.* Sundelin, 1941) and arsenicals (arsphenamine) may cause exfoliative dermatitis, endogenous conjunctivitis, stomatitis, and varying joint symptoms, very much like exudative erythema multiforme (Edmund). The disseminated exanthema, polyarticular lesions, and mucosal symptoms of serum disease are well known.

CONCLUSION

It is hardly possible to draw any definite conclusions, because our knowledge of many of the clinical pictures mentioned above is still rather limited. But it appears from the present clinical

analysis that a group of the rheumatic joint diseases, which—except uratic arthritis—all belong to the type of infective arthritis, are to a certain extent associated with eye symptoms, chiefly of an allergo-toxic nature. The eye and joint disease may be presumed to have the same aetiology and pathogenesis, where either a definitely known or a supposed primary bacterial (or virus) infection releases the allergo-toxic symptoms. The many clinical points of resemblance to various generalized diseases located on the skin, the pluri-orificial mucous membranes, and the joints, where allergo-toxic pathogenesis is certain or likely, bear out the hypothesis of an allergo-toxic pathogenesis of concurrent eye and joint diseases in a more restricted sense.

The therapeutic consequences of the above lines will not be discussed further in this place. The underlying bacterial diseases respond to treatment with sulphonamide and penicillin, whereas this has no influence on the supposed virus diseases. Although histamine is only symptomatic of the allergic process, it may be of interest to attempt an anti-histamine treatment (benadryl, pyribenzamine, and antistine). This has been tried on iritis without joint symptoms (Lemoine, 1947) with encouraging results, which, however, need further testing. The favourable response of sanocrysin intoxications to BAL (Cohen, 1947; Edström, 1948) might perhaps prompt one to the use of BAL against some of the related diseases mentioned here.

SUMMARY

A clinical analysis is given of the incidence and symptomatology of concurrent eye and joint diseases. The medical joint diseases which are complicated by eye symptoms (phlyctenular conjunctivitis, scleritis, iritis, and kerato-conjunctivitis sicca) all belong to the type of infective arthritis, partly acute and partly chronic (rheumatic fever, gonorrhoeal arthritis, Reiter's disease, Still's disease, and ankylopoietic spondylitis). The pathogenesis is presumably the same for the eye disease and the joint disease, being probably an allergo-toxic reaction to a primary bacterial or virus infection. This hypothesis is borne out by clinical points of resemblance to various generalized diseases affecting joints, skin and pluri-orificial mucous membranes (conjunctivitis, stomatitis, and affection of external genitals), where an allergo-toxic pathogenesis is certain or likely—Stevens-Johnson's syndrome, Behcet's syndrome, foot-and-mouth disease, serum disease, acute disseminated erythematous lupus, and intoxication by heavy metallic salts, notably sanocrysin and arsenicals.

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OX VITREOUS HUMOUR. 2.—HYALURONIC ACID RELATIONSHIPS*

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INTRODUCTION

This paper is a report of experiments bearing on the state of hyaluronic acid within the ox vitreous humour and the interrelationships, both chemical and structural, between it and the soluble and insoluble proteins of the humour. Isolation of hyaluronic acid from ox vitreous humour by Meyer and Palmer (1934) naturally gave rise to the idea that this viscous polysaccharide is concerned with the maintenance of the vitreous body. Meyer and Palmer isolated it in a concentration of about 0·05 per cent. from ox vitreous humour filtrate and although Meyer, Smyth and Gallardo (1938) showed that the humours of other animals did not contain so much, yet it is obviously an important constituent of all that have been so far examined. In the ox vitreous humour there is more hyaluronic acid than soluble or insoluble protein. Table I gives values for the concentration of hyaluronic acid and the proteins of the vitreous humours of ox and man and demonstrates the great dilution in which they occur.

TABLE I.—COMPOSITION OF VITREOUS HUMOUR

Vitreous humour	Ox	Man	Ox	Man
	mg/100 ml.		mg/single humour	
Total nitrogen	22–24[1]	23·5[2]	3·9–4.3	0·9
Soluble protein	39–43[1]	20–40[3]	7–8	0·78–1·56
Residual protein	11–16[3]	—	2–3	—
Hyaluronic acid, calculated from hexosamine ...	41[3]	9·9[2]	7·5	0·38
,, ...	—	11·5–19[3]	—	0·44–0·75

The volume of a single ox vitreous humour is taken as 18 ml.
The volume of a single human vitreous humour is taken as 3.9 ml. (Tab. Biol. 1947).
[1]Krause (1934).
Meyer, Smith and Gallardo (1938).
[3]Own results.

* Received for publication, September 11, 1948.

The vitreous humour has been described in many different ways; histologists, physical chemists and ophthalmologists each have a different approach to the problem, which is basically to account for the stability of a structure which contains such low concentrations of its constituents. A study of the residual protein of the ox vitreous humour by Pirie, Schmidt and Waters (1948) led them to consider that the picture given by the histologists most nearly fitted their biochemical findings. According to this view, the vitreous humour is a tissue made up of a network of fibrils which are the prolongations of cells and this network is permeated by a viscous fluid, or jelly, which easily flows out of it. Pirie, Schmidt and Waters found that hydrolysis of the fibrillar protein by enzyme preparations containing collagenase caused liquefaction of the humour. This protein, however, occupies only a minute part of the total volume of the humour which is made up of a viscous solution or jelly of hyaluronic acid, soluble proteins derived from the blood and substances of small molecular weight.

Breakdown of this may also be expected to cause pathological changes in the humour. For example, it seems possible that disaggregation of the hyaluronic acid to a non-viscous form might also lead to disorganisation of the fibrillar network, perhaps with production of visible opacities, such as those seen in senile degenerations of the humour. It is well known that substances diffuse through the vitreous humour *in vivo* with extreme slowness. Haemorrhages remain localised for long periods and von Sallmann, Meyer and di Grandi (1944) found that penicillin injected intra-vitreally diffused through only one-third of the volume of the humour in 6 hours. This lack of spread may be due either to the way in which the fibrillar protein is laid down, or to the inhibiting effect on the diffusion of large molecules by the hyaluronic acid jelly. Probably both play some part and one might therefore expect that a change in the state of either would be reflected in changes, both in the state and in the behaviour of the vitreous humour. As a first step in the experimental consideration of these inter-relations, a study has been made of the state of hyaluronic acid in the normal ox vitreous humour and of the effect of hyaluronidase, the enzyme system that disaggregates and hydrolyses hyaluronic acid, on the behaviour of ox vitreous humour *in vitro*.

The state in which hyaluronic acid exists in the tissues and fluids of the body is not yet clear. Evidence derived from electrophoresis seems to show that it is not combined with protein at the pH of the body, but exists free, presumably as an ion. For example, Blix (1940) found that electrophoresis of filtered, dialysed and concentrated ox vitreous humour caused the hyaluronic acid

to migrate in the electric field faster than any of the proteins present. Meyer and Chaffee (1940) found that the hyaluronic acid of a viscous fluid obtained from a tumour behaved in the same way, yet many workers have been impressed by differences in physical properties between the native fluids of the body and hyaluronic acid solutions of comparable strength. For example, the viscosity of the tumour fluid studied by Meyer and Chaffee was far greater than the viscosity of solutions of hyaluronic acid of equal strength, perhaps showing that hyaluronic acid is combined with protein in the native fluid. On the other hand, it is possible that this difference in the viscosity of the native fluids and of solutions of hyaluronic acid isolated from them lies only in the different degree of aggregation of hyaluronic acid in the two situations.

Blix and Snellmann (1945) found that hyaluronic acid prepared from different sources had very different particle lengths, or degrees of molecular aggregation and that even hyaluronic acid from a single source might be polydisperse. For example, the material prepared from ox vitreous humour had particle lengths varying from 1,000 A° to 4,800 A°, judging from viscosity measurements. Hadidian and N. W. Pirie (1948) have recently isolated highly aggregated hyaluronic acid from umbilical cord with a relative viscosity greater than that of any previous preparations and they speak of hyaluronic acid as a family of substances differing slightly in architecture and greatly in particle size.

Consideration of the state of hyaluronic acid in the vitreous humour may, therefore, be directed to determine whether it is free or combined with protein and whether it is highly aggregated and, therefore, possibly immobile within the humour structure, or relatively disaggregated and freely diffusible. Meyer (1947) has suggested that hyaluronic acid is formed in the ciliary body and circulates in the vitreous humour, finally escaping into the aqueous humour, where it is disaggregated by hyaluronidase. Knowledge of the state and mobility of hyaluronic acid in the vitreous humour should help to evaluate these very interesting suggestions.

METHODS

State of aggregation of hyaluronic acid. Aggregated hyaluronic acid gives a fibrous precipitate with protein in dilute acid or acid acetone. Disaggregated hyaluronic acid gives either a flocculent precipitate or cloud under these conditions. This difference in precipitability has been used to estimate the disaggregating, or mucinase, effect of hyaluronidase and other systems by Robertson, Ropes and Bauer (1940). In the absence of protein, hyaluronic acid is not precipitated by dilute acid, but comes down with acetone. Aggregated hyaluronic acid gives a fibrous precipitate and disaggregated a flocculent one. I have used the change in type of precipitate with acid acetone as a qualitative test for the degree of aggregation of hyaluronic acid. The presence of 75 per cent. of the aggregated

form masks the presence of 25 per cent. of the disaggregated acid, but the test is sufficient to show any major disaggregation. The solution to be tested is acidified with dilute acetic acid and added to 2-3 vol. acetone. A fibrous clumped precipitate in a clear fluid is characteristic of aggregated hyaluronic acid, while a cloud or flocculent precipitate shows that the acid has been disaggregated.

Hexosamine was estimated by the method of Elson and Morgan (1933) and total nitrogen by micro-Kjeldahl followed by distillation and titration, using the apparatus described by Markham (1942). Total carbohydrate was estimated by the orcin colorimetric method described by N. W. Pirie (1936); this estimates the glucuronic acid but not the hexosamine part of the hyaluronic acid molecule.

MOBILITY OF HYALURONIC ACID THROUGH VITREOUS HUMOUR

Ox vitreous humour contains both proteins and hyaluronic acid in solution. Friedenwald and Stiehler (1934) found that all soluble organic material could be removed from a humour by prolonged washing in saline. It is, therefore, possible for hyaluronic acid to diffuse through and escape from the humour, but whether it does so combined with protein, or as an independent entity is not known. An attempt to answer this was made by analysing the material that stayed within the humour after varying times of washing. If protein and hyaluronic acid diffused out independently, then the composition of the material remaining should vary according to the time of washing.

Ox vitreous humours taken out of the eye ½—2 hours after death were suspended in water or saline for varying periods in the ice chest. The washing fluid was changed each day and finally the vitreous humour was filtered and the filtrate precipitated with acid acetone. The composition of this precipitate was compared with that from an ox vitreous humour filtered immediately after removal from the eye. In this way the rate of escape of protein and of hyaluronic acid could be roughly estimated. In some cases the composition of the precipitate from the washing fluid was also investigated. The first wash waters contained considerable salt and gave a flocculent precipitate with dilute acetic acid, indicating the presence of protein and hyaluronic acid which precipitate as a mucin compound in the dilute acid. The later wash waters contained no salt, no mucin and only traces of material precipitable by acetone. In contrast with this, the filtrates of fresh humours gave acetone precipitates with a carbohydrate content of 9—12 per cent., while filtrates of well-washed humours gave acetone precipitates with a carbohydrate content of 14—38 per cent. The acetone precipitate from the filtrate of a fresh humour after dialysis in a cellophane sac had a carbohydrate content of 14 per cent. This shows that the protein in the ox vitreous humour washes out more easily than the carbohydrate hyaluronic acid. This was further demonstrated by an experiment in which a single vitreous humour was suspended in water for

eight days, the water being changed each day. The wash waters were combined, concentrated and then added to acid acetone. The precipitate was centrifuged off, dried, weighed and its carbohydrate content was determined. On the eighth day the vitreous humour was filtered and the filtrate precipitated with acetone and the precipitate analysed in the usual way. The acetone precipitate from the collected wash waters weighed 17·8 mg. and contained 7·1 per cent. carbohydrate, while the acetone precipitate from the filtrate weighed 9·2 mg. and contained 20·4 per cent. carbohydrate. Table II gives the analysis of the acetone precipitates from the

TABLE II.—COMPOSITION OF ACETONE PRECIPITABLE MATERIAL FROM THE FILTRATE OF OX VITREOUS HUMOUR AFTER VARIOUS TIMES OF WASHING THE HUMOUR IN H_2O.

Washing time days	Wt. Precipitate from 1 humour mg.	Total N %	Total Carbohydrate (Glycuronic Acid — as glucose) %	Hexosamine %
0	19·8	—	10·1	—
0	20·7	—	9·2	—
0	—	6·7	12·6	11·3
0	—	6·5	—	7·6
3	15·9	—	14·6	—
9	6·5	—	14·6	—
14	>4·0	—	19·0	—
22	3·6	7·0	24·0	19·5
28	7·6	7·5	38–43	24·0
approx. 1 month	3·7	7·1	—	12·1
,,	—	6·3	23·0	24·4
,,	—	6·4	19·5	26·6
Dialysed fresh filtrate	15·9	7·9	14·6	16·6
Hyaluronic acid Meyer & Palmer (1936)	—	3·37	46·8	43·1

vitreous humours after various washing times and shows that there is a progressive increase in the carbohydrate content of the material remaining within the humour. The same progressive increase in the carbohydrate content of the relatively immobile material occurred when the vitreous humour was washed in 0·9 per cent. saline rather than in water.

The ash content of the acetone precipitate from fresh humours was 13—17·7 per cent. while that from a washed humour was 4·9 per cent. Calculation, on an ash free basis, of the protein and hyaluronic acid contents of these precipitates shows that the precipitate from a fresh humour has roughly 36 per cent. protein and 25 per cent. hyaluronic acid and the precipitate from a washed humour has 31 per cent. protein and 50 per cent. hyaluronic acid. This means that these experiments have not shown that protein and hyaluronic acid wash out quite independently of each other, but have demonstrated that they are relatively independent and that no compound similar to a mucin exists in the vitreous humour.

Two further points of interest arise from these experiments. The washing fluids from the vitreous humours always gave flocculent precipitates, either with acid alone or with acid acetone, whether the volume of the fluid was large or purposely kept small. This means that under the conditions of the experiment, aggregated hyaluronic acid does not diffuse out of the vitreous humour. All that diffuses is already disaggregated. The instability of aggregated hyaluronic acid is well known and Robertson, Ropes and Bauer (1940) showed that vitreous humour filtrate contained a disaggregating system, which they identified as ascorbic acid. It seems probable that gradual disaggregation of the hyaluronic acid goes on during washing. The material which stays within the washed humour and can be filtered out is always in the aggregated form giving a fibrous precipitate with acid acetone. This supports Meyer's idea of a circulation of hyaluronic acid in the eye with final escape through the aqueous humour of the disaggregated material.

A second point of interest is that the filtrate from a washed vitreous humour is not uniform in composition. After 7—10 days in repeated changes of distilled water, ox vitreous humour swells to 2—4 times its original size. Such swelling has already been described by Goedbloed (1935). I found that the filtrate from such swollen humours varied in composition, the first part, coming presumably from the outer part of the humour mass, being almost free from precipitable material and the last 5—10 ml. containing highly aggregated hyaluronic acid. This implies either that there is an internal structure of the vitreous humour, or that the jelly

of hyaluronic acid and protein is broken down gradually, the outer parts being washed away first. The very unstable character of the vitreous humour jelly makes this second explanation seem improbable and I think that this experimental finding is in favour of the view that there is an internal network which impedes to a certain extent the movement of large molecules.

INFLUENCE OF STRUCTURAL PROTEIN ON STATE OF HYALURONIC ACID

The action of hyaluronidase on the vitreous humour in the eye and excised from the eye and on the vitreous humour filtrate was studied in order to see whether the presence of the vitreous structure influenced in any way the action of the enzyme on the contained hyaluronic acid. The enzyme preparations were injected into the vitreous humour with a hypodermic syringe and the eyes, or the extracted humours or filtrates, were then incubated at 37° for varying times. Humours injected with saline were incubated to control the spontaneous disaggregation of hyaluronic acid. After incubation the vitreous humours were filtered directly into acid acetone in order to stop enzyme action and get immediate precipitation of mucin. The activity of the enzyme was judged by the type of precipitate obtained, a fibrous precipitate showing that the hyaluronic acid was still aggregated and a flocculent precipitate showing that the enzyme had disaggregated it. In some cases the insoluble residues from the humours were washed, dried and weighed in order to measure whether hyaluronidase had any effect on the residual protein.

Table III gives the results of these experiments and shows that in no case did hyaluronidase liquefy or have any grossly visible effect on the vitreous humour. Blix (1946) has already noted that hyaluronidase does not liquefy vitreous humour. Enzyme preparations that disaggregated hyaluronic acid instantly in the filtrate took a long time to disaggregate it when it was retained in the vitreous humour structure. The enzyme was slowed down even more when acting on the vitreous humour in the eye. This difference in the rate of action of hyaluronidase inside and outside the vitreous humour is probably due to the slow rate of diffusion of the enzyme through the vitreous body. If an injection of enzyme is made into the centre of an intact extracted humour contained in a small pot, the injected enzyme can be seen as a small bubble of different refractive index for several hours after injection. The vitreous humour structure prevents rapid diffusion of substances through it and in this way the structural protein influences the state of hyaluronic acid in the humour and tends to maintain it in the aggregated state.

TABLE III.—EFFECT OF HYALURONIDASE ON OX VITREOUS HUMOUR

Exp: No.	Vitreous Humour preparation	Enzyme prep: injected	Time at 37° hr:	Gross effect	Acetone ppt: from filtrate	Residue Wt: mg.
1	In ox eye	0·1 ml. *Cl. Welchii* preparation 500 v.r.u./ml.	1¾	none	fibrous	—
	Freshly extracted	,,	1½	none	flocculent	—
	Filtrate	,,	none	none	flocculent	—
	In ox eye	none	1¾	none	fibrous	—
	Freshly extracted	none	1½	none	fibrous	—
2	In ox eye	0·5 ml. of 1% Testis extract	15	none	fibrous	4·0
	Freshly extracted	,,	15	none	flocculent	2·6
	In ox eye	none	15	none	fibrous	4·0
	Freshly extracted	none	15	none	fibrous	3·0
3	In ox eye	0·2 ml. Testis preparation 96 v.r.u./ml.	17	none	flocculent	3·0
	In ox eye	none	17	none	fibrous	3·9

One viscosity reducing unit (v.r.u.) of hyaluronidase is that concentration of enzyme that will reduce the viscosity of a standard substrate preparation to a level halfway between its original value and that of the solvent employed in 20 minutes, McClean (1942).

A further demonstration of this came from a study of another disaggregating system. Ascorbic acid, which is present in the normal vitreous humour in a concentration of 50 mg./100 ml. filtrate (Robertson, Ropes and Bauer, 1941), can disaggregate hyaluronic acid. This action is catalysed by copper, and addition of a small amount of copper to the filtrate of the ox vitreous humour caused immediate disaggregation of the hyaluronic acid. If, however, the same amount of copper was injected into the vitreous humour, no disaggregation occurred, even after 12—20 hours' incubation at 37°. This is probably because the copper combines with the structural protein and so becomes non-diffusible and inactive as a catalyst. Here again the presence of the structural protein has an influence on the state of hyaluronic acid.

INFLUENCE OF AGGREGATED HYALURONIC ACID ON DISSOLUTION OF STRUCTURAL PROTEIN BY COLLAGENASE PREPARATIONS

Pirie, Schmidt and Waters (1948) showed that enzyme preparations from *Cl. Welchii* containing collagenase liquefied ox vitreous humour. They found that the liquefied humours always contained disaggregated hyaluronic acid. The enzyme preparations contained no active hyaluronidase, but were found to have 0·043 mg./ml. of Cu and this presumably acted as a catalyst for the disaggregation of hyaluronic acid by ascorbic acid in the liquefying humour. Table IV shows the disaggregating effect of the enzyme preparation and shows that disaggregation can be inhibited by addition of sodium diethyl dithiocarbamate which combines with copper and makes it catalytically inactive. Experiment 3 shows that the enzyme preparation does not disaggregate hyaluronic acid from umbilical cord unless ascorbic

TABLE IV.—DISAGGREGATION OF HYALURONIC ACID BY *Cl Welchii* COLLAGENASE PREPARATIONS

Expt. No.	Substrate	Saline added ml.	Enzyme added ml.	Time hr. 20°	Type of Acetone precipitate from filtrate
1	5 ml. ox vitreous humour filtrate	0·2	—	23	fibrous
	ditto	—	0·2	23	flocculent
2	2 ml. ox vitreous humour filtrate	0·1	—	5	fibrous
	ditto	—	0·1	5	flocculent
	ditto	—	0.1 +0.05 ml. 0.5% sodium diethyl dithiocarbamate	5	fibrous
3	1·0 ml. 0·9% hyaluronic acid (umbilical cord)	—	0·05	3	fibrous
	1·0 ml. 0·9% hyaluronic acid (umbilical cord) + M/3000 ascorbic acid	—	0·05	3	flocculent
	1·0 ml. 0·9% hyaluronic acid (umbilical cord) + M/3000 ascorbic acid	—	—	3	fibrous

TABLE V.—EFFECT OF AGGREGATED HYALURONIC ACID ON COLLAGENASE ACTIVITY

The enzymes or other solutions were injected into the vitreous humours which were incubated overnight at 37° in the presence of toluene in small glass pots. 0·2 ml. 0.5 % sodium diethyl dithiocarbamate was used in experiments 1 and 2 and 0·3 ml. 1% in experiment 3. 0·3 ml. or 0·4 ml. collagenase containing 22 Q units of activity/ml. was used and 0·2 ml. testicular hyaluronidase containing 96 viscosity reducing units/ml.

Addition to vitreous humour	Gross effect	Type of acetone precipitate from filtrate	Weight of residue after filtration mg.
Saline	none	flocculent	3·6
Saline plus dithiocarbamate	none	fibrous	3·2
Collagenase ...	fluid	flocculent	none
Collagenase plus dithiocarbamate	mainly solid	fibrous	2·1
Saline	none	fibrous	3·8
Saline plus dithiocarbamate	none	fibrous	3·4
Collagenase ...	half fluid	flocculent	2·2
Collagenase plus dithiocarb mate	quarter fluid	fibrous	2·6
Saline plus dithiocarbamate	none	fibrous	1·5
Collagenase ...	part liquid	part fibrous	2·0 (very fragile)
Collagenase plus dithiocarbamate	solid	fibrous	1·8
Collagenase plus dithiocarbamate plus hyaluronidase	part liquid	flocculent	1·8 (very fragile)
Hyaluronidase ...	solid	flocculent	3·0
Hyaluronidase plus dithiocarbamate	solid	flocculent	3·0

acid is added. Both copper and ascorbic acid must be present for disaggregation to take place.

Mixture of diethyl dithiocarbamate with the collagenase preparation before injection into the vitreous humour slowed down

the liquefaction of the humour and the digestion of the insoluble protein. This effect is not due to inhibition of collagenase by the dithiocarbamate as corneal collagen is dissolved by collagenase in its presence. It seemed probable that dithiocarbamate prevented disaggregation of hyaluronic acid in the humour, and that aggregated hyaluronic acid prevented the spread of the collagenase through the vitreous humour mass, and so slowed down liquefaction.

I tried to verify this assumption by determining whether the inhibition of liquefaction by dithiocarbamate could be nullified by hyaluronidase. The experimental results were not entirely clear-cut, but showed that on the whole the addition of hyaluronidase to a mixture of collagenase and dithiocarbamate increased the liquefaction of the humour. In these experiments it was difficult to adjust the time of incubation so that no spontaneous disaggregation took place and yet the added hyaluronidase had sufficient time to disaggregate all the hyaluronic acid throughout the humour. The earlier series of experiments with hyaluronidase (Table III) had shown that the enzyme only acted slowly in the intact humour. Table V gives the results of three typical experiments, showing the inhibitory effect of dithiocarbamate on liquefaction and the effect of hyaluronidase on this. The last column records the weights of the insoluble residues from the humours after complete filtration. These residues were washed by suspension in water overnight whenever this was feasible, but in some cases they were so flimsy that this could not be done, and they were dried without washing, which means that the dry weight is probably too big.

DISCUSSION

The results of the experiments reported in this paper show that the soluble proteins wash out of the vitreous humour more easily than the hyaluronic acid, but that hyaluronic acid cannot be completely separated from protein in this way. The experiments do not therefore rule out the possibility that a compound of hyaluronic acid and protein occurs, but suggest that, if this is so, it is unlike the mucin type of compound obtainable by co-precipitation of hyaluronic acid and protein in dilute acid, where the hyaluronic acid forms a small part of the molecule.

Although hyaluronic acid and the insoluble collagen-like protein of the vitreous humour do not seem to have any chemical relation in the humour, yet they do influence each other. Aggregated hyaluronic acid has a very large particle size, and the hyaluronic acid-containing jelly of the vitreous humour may be considered as

an unstable structure that inter-acts with the structure of the insoluble protein. Liquefaction of the insoluble protein is slowed down by the presence of aggregated hyaluronic acid, and dis-aggregation of hyaluronic acid is slowed down by the presence of the insoluble protein. Each structure tends to preserve the other, and it seems possible that pathological changes in one might also lead to change in the other.

These experiments have been made on ox vitreous humour only. Meyer, Smyth and Gallardo (1938) have shown that the amount of hyaluronic acid is 3—4 times greater in the ox than it is in other animals. Von Sallmann (1948) has found that injection of hyaluronidase into the rabbit's eye causes partial liquefaction of the vitreous humour, and that the spread of injected haemoglobin in rabbit vitreous humour is accelerated by hyaluronidase. There are therefore big species-differences in the structure and behaviour of the vitreous humour, but it is likely that, even in species that have less hyaluronic acid in their vitreous humour than the ox, one must take into account the structural inter-actions between the collagen-like insoluble protein and the hyaluronic acid jelly when considering the biological behaviour of the vitreous body.

SUMMARY

1. Suspension of ox vitreous humour in water washes out protein and hyaluronic acid at different rates, and the analysis of the material remaining within the humour shows that there is no compound comparable to a mucin present in the humour.

2. Hyaluronidase acts more slowly within the vitreous humour than in the vitreous humour filtrate.

3. Collagenase preparations are inhibited by aggregated hyaluronic acid in the vitreous humour.

4. The conclusion is drawn that the presence of the insoluble structural protein of the humour may help to maintain aggregated hyaluronic acid, and that aggregated hyaluronic acid may help to maintain the structural protein.

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LEIOMYOMA OF THE IRIS*

Report of a Case

BY

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THE clinical and pathological diagnosis of tumours of the iris presents many difficulties. Because of their rarity it falls to the lot of few observers to have more than a passing acquaintance with them. Fear of their possible malignancy warps the judgment of the surgeon, and neither the clinician nor the pathologist approaches the problem with an unbiassed mind.

In 1943 Kahler, Wallace, Irvine and Irvine reported "the seventh case of leiomyoma of the iris." Following the lead of Verhoeff, several reported myomata of the iris and ciliary body were rejected because of insufficient histological proof. On the other hand, it is not unlikely that many cases have been wrongly labelled leuco-sarcoma (unpigmented melanoma) because their real nature was not apparent with the usual haematoxylin and eosin stain. Van Gieson's stain and Mallory's connective-tissue stain show that the tumour cells take the stain characteristic of

* This case was presented at a meeting of the clinical society, St. Vincent's Hospital, Melbourne, Victoria, Australia, on March 22, 1948. Received for publication, October 25, 1948

Some months ago I forwarded to you a report on a case of leiomyoma of the iris. Just recently, I have seen a report by E. C. Moulton, Senr. and E. C. Moulton, Jnr. from Fort Smith, Arkansas, in the *American Journal of Ophthalmology* for February, 1948 (**31**, 214) in which they report a similar case. They mention the presence of cataract, and make a suggestion similar to mine, that the growth appears in the region of the foetal fissure. I was unaware of their article when I sent my report to you.

muscle. With Mallory's phosphotungstic acid haematoxylin the fibrillary nature of the tumour is apparent. Dense fibrils appear to take their origin from each end of the cell and course for long distances through the tumour without anastomosing. They bear no resemblance to the delicate anastomotic network of processes from the cells of a melanoma.

Clinically they may appear as grey, vascular tumours sessile or pedunculated. They may give rise to hyphaema, or as in the following case to cataract. They may be slow-growing or show periods of activity. Their diagnosis is of more than academic interest as they are benign and can often be completely removed by an iridectomy. For this reason every unpigmented or lightly pigmented tumour of the iris should be treated conservatively or subjected to biopsy before deciding on the fate of the eye. In the following case a clinical diagnosis of unpigmented melanoma was made with some confidence, and the eye removed. The histological findings were those of a leiomyoma.

On 6/1/47 Mrs. A. McH., aged 65 years, complained that the sight in the right eye had been failing for the previous twelve months. The vision in the right eye was 6/36, and could not be improved. The vision in the left was 6/12 and improved to 6/6. There was a sessile, unpigmented grey tumour occupying nearly the whole of the outer lower quadrant of the right iris. The outer edge was hidden by the limbus. It was very vascular and surrounded by a gelatinous fringe spreading over the surface of the surrounding iris. At the margin of the pupil there was a little ectropion of the pigment epithelium. The edge of the pupil appeared to be lifted forward, bringing the posterior surface of the iris into view and revealing a radial band of atrophy of the pigment epithelium. The lens was opaque behind the tumour, and the opacity was spreading across the pupil, obscuring the details of the fundus. The tension was normal, and remained so after the pupil had been dilated with homatropine and cocaine. The pupil dilated almost fully, and there was little evidence of distortion where the tumour abutted on the pupil. The most probable diagnosis appeared to be an unpigmented melanoma (leuco-sarcoma). The absence of rigidity of the iris, and the atrophy of the pigment epithelium introduced an element of doubt. The vascularity of the tumour, and the lens opacity which appeared to be caused by it were thought to be in favour of the diagnosis of malignancy. Iridectomy was not considered because it was probable that the tumour had already infiltrated the ciliary body, so that removal would not be complete.

The eye was removed, fixed in Zenker's fluid, embedded in celloidin, and sections stained in haematoxylin and eosin, van Gieson, Mallory's connective tissue stain, Mallory's phosphotungstic acid haematoxylin and Wilder's reticulin stain. The sections showed a tumour (Fig. 1) extending from the pupil to the base of the iris and beginning to invade the ciliary body. It appeared to occupy the interstices of the iris, compressing the normal tissues rather than infiltrating them. The posterior surface of the iris was curved backwards, dimpling the lens where it had caused proliferation of the sub-capsular epithelium (Fig. 2), and destruction of the fibres beneath. The pigment epithelium

FIG. 1

Mallory's connective-tissue stain. The more darkly staining area is the compressed iris tissue.

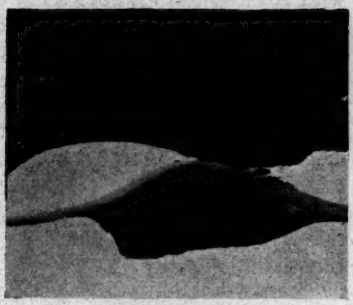

FIG. 2

Mallory's connective-tissue stain. Atrophy of pigment epithelium. Proliferation of subcapsular epithelium of the lens.

FIG. 3

Haem. and eosin. section through the gelatinous fringe. Tumour cells growing along the anterior surface of the iris, and a large new vessel.

FIG. 4

Haem. and eosin. Base of the iris. Infiltration with round cells. Swollen tumour fibrils in the lower right-hand corner above the pigment epithelium.

of the iris had disappeared at the posterior limit of the curve. Anteriorly the tumour had compressed the normal iris tissue. There was no evidence that it was actually infiltrating this structure, but it had escaped through the openings of the crypts. Sections cut at the edge of the tumour showed a thin layer of tumour-cells spreading over the surface of the iris (Fig. 3), and accounting for the gelatinous fringe seen clinically. At the base of the iris there was evidence of a recent haemorrhage being absorbed in one of the crypts. Where the tumour was invading the ciliary body there was a collection of small round cells with some oedema (Fig. 4). The tumour was composed of bundles and

whorls of spindle-shaped cells ending in long fibrils (Figs. 5 and 6). The nuclei were rod-like and arranged in the so-called palisade formation. In some areas where the bundles were cut transversely (Fig. 6), many nuclei were to be seen in the one section. In others, the nuclei were very few in number, and the bundle composed mainly of fibrils. The chromatin of the large cylindrical nuclei was scattered in fine granules with one or two more dense aggregations. No mitotic figures were seen. Very little protoplasm could be seen surrounding the nuclei except in those cells lying near the dilator muscle. Here each end of the cell tapered off rapidly to a coarse fibril which could often be followed across several high-power fields. There was no evidence of any anastomosis with neighbouring fibrils. Its thickness did not always remain constant, and it would often present a marked fusiform dilatation at some distance from the nucleus. In the main mass of the tumour the amount of the protoplasm surrounding the nucleus was greatly reduced, and the fibrils appeared to split to surround it. The swelling of the fibrils was seen everywhere, even in the isolated bundles of cells creeping round the base of the iris to invade the ciliary body (Fig. 3). In cross-section it appeared as a circular homogeneous mass (Fig. 6). The cell body, fibril and dilatation stained a uniform pink with eosin, yellow with van Gieson, red with Mallory's connective-tissue stain, and a deep violet with the phosphotungstic acid haematoxylin, in contrast in the latter case with the red tinge of the violet of the connective tissue of the iris. Mallory's connective-tissue stain showed that the connective tissue in the section belonged to the compressed iris. There was little evidence of new formation of connective tissue between the tumour cells, and no reticulin. There were several large blood vessels in the tumour, and many fully formed capillaries with connective-tissue walls. None was embryonic in type. The pigment content of the tumour was small and confined to the compressed iris tissue, where chromatophores were present (Fig. 7). Pigment-laden cells, probably phagocytes, were present in large numbers in the spaces of the pectinate ligament in both angles. In the general picture seen with Mallory's connective stain, and with that of Wilder, it was obvious that the tumour had compressed the normal tissue, and if it had not found a way out through the crypts of the iris and through the loose tissue of the base of the iris, it would have become encapsulated thereby (Figs. 1 and 7). The compression of the superficial tissues of the iris was so marked that, when stained with haematoxylin and eosin, the cells of the anterior border layer formed a distinct line in the depth of the tumour right across the section (Fig. 6). The tumour had all the characteristics of a leiomyoma.

FIG. 5

Mallory's phosphotungstic acid. Posterior section of the iris. The pigment epithelium is at the lower edge.

FIG. 6

Haem. and eosin. The anterior border layer runs from the lower left to the upper right-hand corner. The anterior surface is above this diagonal. A transverse section of a bundle of fibrils in the lower right-hand corner shows many fibrils of varying thicknesses and few nuclei. Comparatively more nuclei are present in the upper left-hand bundle.

FIG. 7

Wilder's reticulin stain. Ectropion of pigment epithelium with tumour cells growing over it and also splitting it. Reticulin is apparent only in the compressed iris tissue. The tumour has reached the surface through the orifice of a crypt.

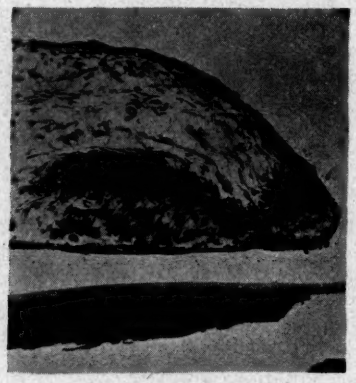

FIG. 8

Region of the sphincter on the side of the pupil opposite the tumour. Haem. and eosin. Atrophy of pigment epithelium. Proliferation of cells of dilator. Collection of chromatophores and pigment-laden phagocytes.

There was some atrophy of the pigment epithelium of the iris posterior to the sphincter muscle on the side of the pupil opposite the tumour (Fig. 8). This was associated with proliferation of the cells of the dilator muscle in that region. There was an abnormal appearance of chromatophores in the area, as if they were migrating forwards into the sphincter muscle. There were other round pigment-laden cells, probably phagocytes, in the vicinity, some in the space between the sphincter and the dilator, others on the posterior surface of the iris. This may have been an early nodule of tumour of the dilator muscle distinct from the main mass.

COMMENT

It is impossible to say from which muscle the tumour arose. Some sections appeared to show the cells of the dilator muscle elongating, gradually losing their pigment content, and merging into a general stroma of the tumour. Four factors call for special comment:—

1. The presence of haemorrhage. Van Duyse comments on this with the remark that intra-ocular haemorrhage in the presence of tumour does not necessarily indicate malignancy.

2. The presence of inflammatory exudate where the tumour was invading the ciliary body. In addition, an occasional ghost cell was seen along the posterior surface of the iris.

3. The presence of proliferation of the subcapsular epithelium of the lens due directly to the pressure of the tumour.

4. The presence of fusiform dilatations along the fibrils of the tumour. These receive no mention in the reports of Verhoeff, Frost, Ellett and Kahler *et al.* Van Duyse refers to a hyaline degeneration of the cell protoplasm seen in sections stained with Van Gieson and most obvious in transverse sections. He gives no reason for his assertion that hyaline degeneration was present. He also comments on the contrast between the yellow colour of the tumour fibrils which assimilate the picric acid of the van Gieson and the red of the connective tissue nearby, stained with fuchsin.

SUMMARY

A further case of leiomyoma of the iris is described. The clinical history and appearance vary greatly. Those of van Duyse, Verhoeff and Ellett had a history of twenty years' duration, that of Kahler *et al.* two, and of Frost only one. At

the time of operation the patient of van Duyse was twenty-eight, of Verhoeff thirty-three, of Frost forty-six, of Ellett forty-seven, and of Kahler *et al.* forty-six. In each case the tumour was on the lower part of the iris, one in the lower nasal quadrant, one in the middle, and four (including the above) in the lower temporal quadrant. In the case reported by Verhoeff the tumour was suspended from the anterior surface of the iris by a narrow pedicle. The remainder presented as sessile tumours which appeared to originate from the depths of the iris. All were vascular, and several were prone to recurrent haemorrhage. van Duyse records that his patient had nine hyphaemas before iridectomy was performed. The only record of cataract is in the present case.

The site of the tumour calls for comment. Although the number of cases is too small to allow sure conclusions, it is remarkable that all were situated in the lower half of the iris. This would suggest that the tumours had arisen near the foetal fissure, and that their origin may be traced to a defect arising at the time of its closure. Verhoeff states that in his case the tumour was "nowhere connected with the iris muscles or pigment epithelium" and that it seemed likely "that it originated from stroma cells of the embryonic uvea, possibly from misplaced cells which ordinarily would have taken part in the formation of the ciliary muscle." The situation of the tumour in all cases reported adds some weight to his suggestion.

ACKNOWLEDGMENTS

I wish to thank Dr. Andrew Brenan, Director of the Pathological Laboratory at St. Vincent's Hospital, Melbourne, for affording me the facilities to investigate this case, Miss Thornton for preparing the sections, and Mr. E. Matthei, Director of the Faculty Workshops at the University of Melbourne, who prepared the photo-micrographs.

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RECESSION OF THE INFERIOR OBLIQUE*

BY

IVOR LLOYD

BRADFORD

Introduction. Vertical imbalance of the eyes related to abnormalities of the inferior oblique is receiving ever-increasing attention, and the accumulation of the results of surgical intervention for the cure of the condition already enables an opinion to be offered as to the effectivity of such treatment.

Overaction of the inferior oblique has interested surgeons for many years, and in certain types of case its cause is still in doubt. Particularly is this so in its relationship to the horizontal squints in children. Doubtless many cases of overaction are due to a paresis of a superior oblique or a superior rectus, but there still remain a number which cannot be explained so readily. The writer tends to the belief that the latter are partly due to a compensatory overaction of the inferior oblique in an endeavour to abduct the eye to counteract excessive convergence by the internal rectus, and probably linked up with a low-grade masked paresis of the external rectus.

It has been the custom to correct the horizontal element in a squint and so far as possible allow the vertical component to right itself, perhaps with the aid of orthoptic exercises. That this procedure is incorrect receives confirmation from many authorities including Spaeth, Gibson, Wheeler, Guibor, Dunnington, Hughes, Wagman, Prangen, Foster and Anderson. Anderson[1] found that 53 per cent. of convergent squints in children were associated with a vertical defect and that 30 per cent. were characterised by overaction of the inferior oblique. The writer reviewed the last 100 cases in his own clinic which required operation for a horizontal defect of convergent type, and found that 48 of them had a vertical defect in addition, which was sufficiently marked as to require operative correction.

It therefore appears to be essential that greater attention should be devoted to the vertical element in the convergent squints. Apart from the cosmetic improvement, which is often considerable, the writer is convinced that in correcting the vertical defect a better functional result is obtained, as the tendency to hyperphoria is eradicated.

Operations on the inferior oblique are not by any means a new thing, but it is only in comparatively recent years that a rational

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approach to the problem coupled with adequate investigation have led to more reliable results being obtained. Wheeler,[2] Wagman,[3] Berens, Conrad and Loutfallah[4] have resected the inferior oblique in cases of paresis of this muscle. White,[5] Guibor,[6] and Prangen[7] have recessed the muscle to correct its overaction.

Tenotomy to reduce overaction of the inferior oblique has been practised for over a hundred years, but the operation has only been used scientifically during the last twenty to thirty years, mainly as a result of improvements in anaesthesia and surgical technique. The transconjunctival route for the operation of tenotomy of the inferior oblique is linked with the name of Guibor, but Landolt described it in 1885.[11] Banister[12] condemned the operation of tenotomy, and it must be conceded that it is only applicable in extreme cases of overaction of the muscle, and that no grading of the result can be obtained. The writer would also add that it deprives the eye of the torsion effect of the muscle. Duane tried a partial tenotomy of the muscle, but was not impressed with the results. The writer has performed this operation on several occasions, and finds that the results are unreliable.

White stated that the indications for reducing the overaction of the inferior oblique were :—

(1) To correct a secondary overaction of the inferior oblique caused by a paresis of the superior rectus of the fellow eye.

(2) To correct a secondary contracture due to a paralysis of the superior oblique of the same eye.

The writer would like to add a further indication, *viz.*, overaction of the inferior oblique associated with a horizontal squint, especially convergent in type, and not always definitely due to paresis of a vertically acting muscle.

In consequence of the unreliability of partial tenotomy of the muscle, and the fact that a full tenotomy could not produce a graded result, attempts were made to recess the muscle. This operation has now been performed by several surgeons, but the number of cases reported is still comparatively small. Despite this the results are so far encouraging. White, Guibor and Prangen have described the technical details of the operation, but do not offer many case-reports.

TECHNIQUE

The surgical approach to the inferior oblique may be either through the lower lid, or by the transconjunctival route. For recession of the muscle the latter method is preferable, as it gives a much better access to the insertion of the muscle, and enables a resection or advancement of the external rectus to be carried out at the

same time, as is so often required. Both Landolt and Guibor favour this approach.

Guibor and White recessed the inferior oblique in such a way as to bring the new insertion further forwards and to some extent downwards, *i.e.*, a true recession as the insertion is made to approximate to the origin. Prangen[7] placed the new insertion 6 to 7 mm. behind the insertion of the external rectus and on the same horizontal line with the latter.

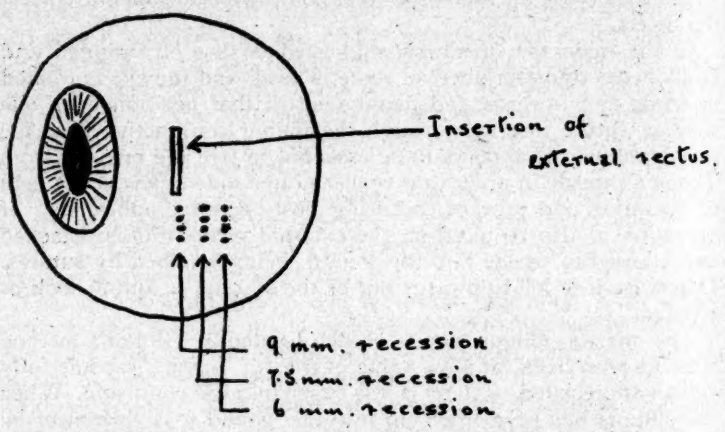
The writer attempted a series of recessions adopting the technique of Prangen, Guibor and White, but found that the effect was very variable and often almost negligible. In consequence the modification described below is suggested. The results of some of the earlier cases were not entirely satisfactory, and this was found to be due to under-correction, *i.e.*, insufficient recession. In the later cases the increased recession proved adequate to correct the defect.

In the main the operation suggested is that of Prangen and Guibor, the transconjunctival route is used, and the eye is rotated upwards and inwards, and maintained in that position by a silk traction suture inserted through the bulbar conjunctiva near the outer limbus. It appears to be essential to free the muscles from Tenon's capsule in order to give an uninterrupted view of the field of operation and prevent confusing post-operative adhesions. If operation is also required on the external rectus this is detached and allowed to recede into the wound, being retained by sutures. Otherwise it is held upwards out of the way by a squint hook or retractor.

The inferior oblique muscle is then located by Guibor's method with a squint hook, and the value of freeing Tenon's capsule fully is then appreciated, as there is less tissue to cause confusion. When the oblique has been lifted up into the wound it is cleared of all extraneous tissue, and the check ligament attaching it to the external rectus is divided. The muscle is then followed up to its insertion, which should be identified with certainty, and a muscle clamp, *e.g.*, Prince's forceps, applied to the tendon close to the insertion in the sclera. Then tendon is then divided. Two catgut sutures are passed through the end of the muscle, one at each corner, and secured with a " whip stitch," and the muscle clamp removed. The sutures are then passed through the superficial layer of the sclera and each one tied separately, so that the muscle is anchored in position. The suturing to the sclera is done in such a way that the knots are one above the other, causing the end of the muscle to be spread out flat with its edge vertical. This seems to give a neater result than the single stitch of Prangen. The conjunctiva is closed, after reattaching the external rectus in

the appropriate cases, using a continuous silk suture. This type of suturing is quite adequate, and renders its removal very much easier, especially in children, than interrupted sutures.

The position on the sclera to which the muscle is attached is further forward than that suggested by Guibor and Prangen. The amount of recession required depends on the pre-operative investigation and measurements. For a full recession the writer has placed the new insertion of the muscle immediately inferior to the insertion of the external rectus, but for lesser effects the muscle may be inserted at varying distances behind this point, but not more than 4 mm., as beyond this the recession appears to be inadequate and unreliable. The line of recession for a graded result is posterior to that for a full recession, and is kept horizontally just below the lower border of the external rectus.



To illustrate the positions for insertion of the left inferior oblique.

It will be seen therefore that, in spite of what Guibor and Prangen advocate, the external rectus need not be detached in order to recess the inferior oblique.

SUMMARY

A review of the operative treatment for overaction of the inferior oblique is presented, and some of the disadvantages of present methods are discussed.

Indications for operation on the inferior oblique are given, particularly in cases of overaction of the muscle.

It is suggested that recession of the muscle is a practicable procedure, and is preferable to partial or complete tenotomy.

CASES OF RECESSION OF INFERIOR OBLIQUE

No.	Age	Type of squint	Operation	Result
1	14	Conv. concom. squint 35° L.E., overaction L.I.O.	L.E. : 5 mm. recess. int. rect. 10 mm. resect. ext. rect. 9 mm. recess. inf. oblique.	Angle of squint + 5° overaction of inf. oblique corrected.
2	5	Conv. concom. squint 25° L.E., overaction L.I.O.	L.E. : 5 mm. recess. int. rect. 8 mm. resect. ext. rect. 6 mm. recess. inf. oblique.	Angle of squint 0° overaction of inf. oblique corrected.
3	5	Conv. concom. squint 30° L.E., overaction L.I.O.	L.E. : 5 mm. recess. int. rect. 10 mm. resect. ext. rect. 9 mm. recess. inf. oblique.	Angle of squint + 5° overaction of oblique corrected.
4	8	Conv. concom. squint 35° L E., L/R 7, bilateral overaction I.O.	L.E. : 5 mm. recess. int. rect. 10 mm. resect. ext. rect. 8 mm. recess. inf. oblique.	Angle of squint 0° L/R 2. No overaction L.I.O. R.I.O. still overacting.
5	7	Conv. concom. squint 35° R.E., overaction R.I.O.	R.E. : 5 mm. recess. int. rect. 10 mm. resect. ext. rect. 6 mm. recess. inf. oblique.	Angle of squint + 5° overaction of R.I.O. corrected.
6	8	Conv. concom. squint 25° R.E., R/L 5., overaction R.I.O.	R.E. : 5 mm. recess. int. rectus. 10 mm. resect. ext. rectus. 8 mm. recess. inf. oblique.	Angle of squint + 5° overaction of inf. oblique corrected.
7	14	Conv. concom. squint 35° R.E., R/L 15., overaction R.I.O.	R.E. : 5 mm. recess. int. rectus. 10 mm. resect. ext. rect. 6 mm. recess. inf. oblique.	Angle of squint + 5° R/L 5. Overaction of inf. oblique corrected.
8	41	R/L 8., overaction R I.O. paresis R.S.O.	R.E. : 7 mm. recess. inf. oblique.	R/L 0° overaction of inf. oblique corrected.
9	5	Overaction L.I.O. paresis L.S.O.	L.E. : 9 mm. recess. inf. oblique.	Angle of squint 0° overaction of inf. oblique corrected.
10	6	Conv. concom. squint 25° L.E., L/R 7., overaction L.I.O.	L.E. : 5 mm. recess int. rect. 10 mm resect. ext. rect. 9 mm. recess. inf. oblique.	Angle of squint + 5° L/R 0° overaction of inf. oblique corrected.
11	7	Conv. concom. squint 5° bilateral overaction of inf obliques.	R.E. : 8 mm. resect. ext. rectus. 9 mm. recess. inf. oblique. L.E. : 9 mm. recess. inf. oblique.	Angle of squint 0° 0/0 No overaction of inf. obliques.
12	7	Conv. concom. squint 30° R.E., overaction of inf. oblique.	R.E. : 5 mm. recession int. rectus. 10 mm. resection ext. rectus. 8 mm. recess. inf. oblique.	Angle of squint + 3° no overaction of inf. oblique.

Evidence is produced that the position for the new insertion of the inferior oblique is important, and that the positions already described for recession of the muscle do not give reliable and accurate results.

The results of cases are given.

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STATISTICAL DATA OF MY CATARACT OPERATIONS PERFORMED WITH A NEW SUTURE OF THE SCLERA

BY

F. PAPOLCZY

BUDAPEST

WHEN studying the history of cataract operations we can see that this most important and most frequent of eye operations has undergone very great changes since the first operations, performed almost 2,000 years ago, up to now. This process, however, was not made equally, but in periods of progress more or less defined by certain great medical discoveries.

The oldest cataract operations which quacks performed during many centuries were depressions or reclinations. They were carried out by inserting a pointed, awl-like needle through the sclera into the eye, and pushing the opaque lens backwards or downwards into the vitreous body. As a consequence of this operation at least 60 per cent. of the patients lost their sight after a longer or shorter time owing to infection, haemorrhage into the vitreous and glaucoma. It often happened that sooner or later, after surgical intervention, the cataract either returned to its original place, or luxation into the anterior chamber took place.

In the middle of the eighteenth century Daviel found out that

much better results could be obtained by removing the cataract through a corneal wound. But after this operation, in 15-20 per cent. of the cases, another complication arose: suppuration of the wound, in consequence of which the eye was often lost.

The perfecting of operative methods, in the present meaning of the word, became possible only when, in the earlier part of the nineteenth century, Davy, Wells, Jackson and others discovered narcosis, and in the latter part of the nineteenth century, local anaesthesia was discovered by Koller and Schleich. Almost simultaneously, Lister found out, on the basis of the research work of Pasteur, that infection caused suppuration of the wound, and that sterilisation and asepsis were the only means of protection against it.

Under these favourable conditions Snellen's cataract operations performed with a conjunctival flap after careful pre-operative treatment were a great advance at the end of the nineteenth century.

At that time everywhere complete iridectomy and extra-capsular operations were done by making a large incision above the iris and then removing the nucleus and cortex as far as possible with a spoon. When, however, part of the capsule and a great part of the cortex remained, inflammation of the operated eye ensued, and it often demanded weeks of treatment. Frequently a dense secondary cataract developed. It was observed that if the capsule forceps was blunt, or the capsule was very thick and resistant, the cataract could be removed together with the capsule. In this case there is no danger of inflammation or after-cataract.

After this experience, Török, Elschnig and Stanculeanu, at the beginning of the twentieth century, devised forceps with which in a great number of cases the cataract could be removed entirely, that is to say with the capsule. Not long afterwards it was found that even better results could be obtained by performing not an entire, but a basal iridectomy, thus leaving the pupil untouched. This led to the round pupil intra-capsular extraction.

The round pupil operation has, however, the disadvantage that in case of rupture of the wound prolapse of a greater or smaller part of the iris can occur, or this may be wedged in the wound. In 1867 Williams found that this complication with its unpleasant and sometimes tragic consequences could be avoided by suturing the wound. The first successful suture was described by Mendoza in 1889. Liégard, in 1913, published a new method which, with a few smaller modifications, still proves useful. Later Kuhnt's conjunctival flap employed by Blaskovics, and Elschnig's, Horváth's and lately McLean's sutures were the most successful and most frequently used.

By using the above-mentioned and many other similar sutures the danger of prolapse of the iris or the iris getting wedged in the wound was considerably diminished, but not completely eliminated. Experience shows that these sutures may bring about certain disturbances or even serious complications regarding the healing of the wound, so naturally ophthalmologists endeavoured to find newer methods which would yield still better results.

The requirements of a suture which is to close the cataract wound well and to ensure its undisturbed healing are :—

1. The suture should not be inserted directly into the corneo-scleral wound, because suppuration of the suture may cause infiltration of the cornea, and wound infection. But it should not be inserted too far from the wound either, because then it is impossible to avoid rupture of the wound with all its consequences.

2. It must unite the edges of the wound exactly in their original place lest gross astigmatism arise.

3. The conjunctival flap must be large enough to cover the wound entirely.

The insertion of the suture should not complicate or unduly prolong the operation, lest ophthalmic surgeons of limited experience should be unable to perform it.

Bearing in mind these considerations and requirements I have now been using for years a new suture for my cataract operations, the original idea of which was given to me by Imre's method. In cases of complicated cataract he made a semi-circular flap into the bulbar conjunctiva, and severing it as far as the limbus turned it back upon the cornea. At 12 o'clock, about 2 mm. from the limbus, he inserted a thread horizontally in the superficial layers of the sclera, then inserted the same thread in that part of the conjunctival flap which was originally above these points. Then pulling the thread out of the wound, he formed a loop. The cataract incision was made in the usual way with Graefe's knife. After extraction the conjunctival flap was replaced upon the sclera, smoothed down, and then the thread was knotted twice.

This method has the disadvantage that, as the detached conjunctiva is elastic and shrinks, it is impossible to insert the suture exactly at the corresponding places in the sclera and the conjunctiva. In consequence the edges of the wound cannot be fixed exactly in their original position. Another disadvantage is that it is very difficult to make the cataract incision after having made and turned back the conjunctival flap previously.

I endeavoured to eliminate these difficulties by inserting the thread through the conjunctiva into the superficial layers of the sclera, and making the incision and the conjunctival flap afterwards. Thus my method is the opposite of Imre's operation.

The following is a detailed description of my operation. After the usual preparation I open the palpebral fissure with Oláh's speculum. The use of this and other similar instruments is of great advantage in intra-ocular operations, because the assistant need not trouble to retract the lids during the whole of the operation.

I fix the eye from above by a suture inserted in the superior rectus, from below by fixation forceps next to the limbus. Then I insert a 6·0 black nylon suture at 12 o'clock, 1 mm. from the limbus, parallel to it through the conjunctiva into the superficial layers of the sclera (Fig. 1). After this I proceed to make the cataract incision with Graefe's knife. But when the corneal part of the incision has been made, and the knife, still under the conjunctiva, has reached the level of the suture, I do not continue the incision, but carefully withdraw the knife from the wound (Fig. 2). Then, above, I make a semi-circular conjunctival flap with scissors, and detaching it from the sclera to the thread, turn it back on the cornea (Fig. 3). After drawing out both threads through the conjunctival tissue with anatomical forceps, I form a loop and cut through the shreds of tissue around the wound with scissors (Fig. 4).

Then after making a basal excision in the iris above, I grasp the capsule from below with Arruga's forceps, and if it is very tense, I use Imre's or Blaskovics' forceps. Afterwards I draw the lens slowly outwards with lateral movements. I expel it by exerting

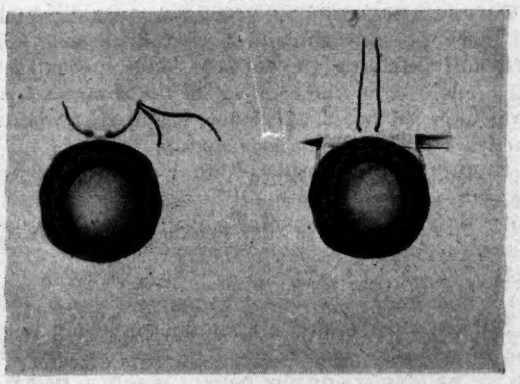

FIG. 1. FIG. 2.

FIG. 1. Insertion of the needle through the conjunctiva into the sclera.
FIG. 2. Making the corneo-scleral incision with Graefe's knife.

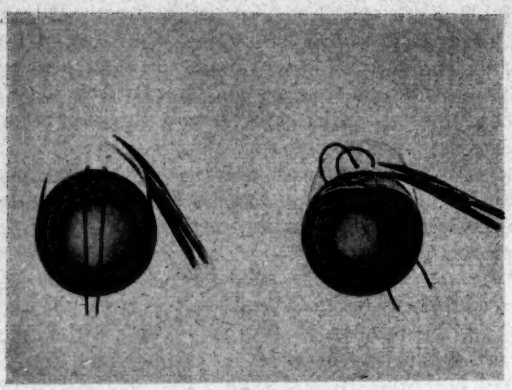

FIG. 3. FIG. 4.

FIG. 3. Making a conjunctival flap with scissors. FIG. 4. The cutting of the subconjunctival tissue, which keeps the wound together.

slight pressure upon the cornea at the lower limbus in the opposite direction with Imre's ring-instrument. I endeavour to remove the cataract by tumbling. If this proves impossible, as for instance with large, flat, hard cataracts, or with a narrow pupil, the assistant lifts the iris slightly off the lens from above with a cyclodialysis spatula or with the finer hook of Horvath's zonulo-ruptor, so that its edge will fit into the pupil. I do not lose hold of the capsule during the extraction. With tumescent or liquefied cataracts, when it is impossible to grasp the capsule, I make a small horizontal incision as recommended by Csillag with a keratome, and subsequently remove the capsule after the extraction; this usually succeeds. After the removal of the cataract I replace the conjunctival flap, smooth it out, knot the thread three times, and replace the iris with a cyclodialysis spatula.

Should rupture of the capsule occur, I remove the remnants of the cortex with a spoon, and finally irrigate the anterior chamber and remove the remnants of the capsule with capsule forceps. I seldom have to make a complete iridectomy after extra-capsular operations.

I cover the operated eye with small squares of gauze, loose cotton-wool and Snellen's perforated aluminium cup, held in place with two straps of adhesive plaster fixed to the forehead and cheek. Both eyes are bandaged and the patient is put to bed for the first day. I change the dressing after 24 hours, and later once a day. The patient may sit up in an arm-chair on the second day. I remove the sutures on the tenth day. Until then the operated eye is kept bandaged.

In the years 1941-1946 I performed 325 senile cataract operations, employing my suture. At first I was not very sure of its success, but after much experience, I have found that this suture has a very favourable influence upon the healing of the wound.

On account of the prevailing opinions, I performed operations with a round pupil only rarely in the beginning, but more and more frequently later on. During the first two years, *e.g.*, in cases of exophthalmos, tumescent cataract, or when the pupil could not be dilated widely enough, or when the other eye had already been operated in this way, and also in cases of extra-capsular operations I made a complete coloboma. The first table shows the results of my operations in 1941-42.

TABLE I

152 operations performed in 1941-1942

INTRA-CAPSULAR		EXTRA-CAPSULAR	
Round pupil	Coloboma	Round pupil	Coloboma
68 =	45 =	15 =	24 =
44.7 %	28.6 %	10.0 %	15.7 %
113 =		39 =	
74.3 %		25.7 %	

Of these WITH ROUND PUPIL: 44.7 % + 10.0 % = 54.7 %
Of these WITH COLOBOMA : 29.6 % + 15.7 % = 45.3 %

During this time I performed 54·7 per cent. operations with a round pupil and 45·3 per cent. with an iridectomy ; 74·3 per cent. were intra-capsular, 25·7 per cent. were extra-capsular operations. At that time I was not yet satisfied with the results of my operations. But later I acquired more practice with this method, and I also found out that the generally accepted opinions regarding operations with a round pupil were out of date. I saw that they could be performed much more frequently without the least danger, even as routine operations. In the following years I made a coloboma only in cases of complicated cataract, prolapse of the vitreous body, or unintentionally, as, for instance, in the case of a markedly tumescent cataract, or if escape of the aqueous floated the iris before the knife. The second table shows the results of my operations performed in 1943-46.

TABLE II

173 operations performed in 1943-1946

INTRA-CAPSULAR		EXTRA-CAPSULAR	
Round pupil	Coloboma	Round pupil	Coloboma
136 =	11 =	22 =	4 =
78.6 %	6.3 %	12.7 %	2.4 %
147 =		26 =	
84.9 %		15.1 %	

Of these WITH ROUND PUPIL : 78.6 % + 12.7 % = 91.3 %
Of these WITH COLOBOMA : 6.3 % + 2.4 % = 8.7 %

During this time I performed 91·3 per cent. operations with a round pupil and only 8·7 per cent. with iridectomy; 84·9 per cent. were intra-capsular, 15·1 per cent. were extra-capsular operations.

My statistics prove that with the help of these sutures I endeavoured always to use the intra-capsular method, and from 1943-1946 with a round pupil; the combination was nearly always successful. In view of these favourable possibilities the indications regarding operation will have to be altered. Nowadays it is not necessary to wait for the cataract to be completely "mature." The operation should be performed as soon as the patient's vision has deteriorated to such a degree that he is unable to carry on his work, or becomes a burden to his family and himself. In many cases I operate for cataract when vision is 5/15 or 5/10 when the patient is a person whose occupation demands good eye-sight, such as mechanics, printers and chauffeurs, etc. When there is cataract in both eyes, I operate first on one eye and only 10-12 days later on the other. Operation can be performed on both eyes then at the same time without the slightest risk or difficulty, but I have found that having both eyes bandaged for several days had a very bad effect on the patients.

The use of my suture makes the operation longer, and for this reason many surgeons are against it. But it is not to the detriment of the patient, and therefore we may not grudge these few minutes if by taking a little longer to operate we are able to improve the results substantially.

The most dangerous complications which may arise during or after cataract operations are loss of vitreous, expulsive

haemorrhage, infection, rupture of the wound, prolapse of the iris, and finally secondary glaucoma. In the older statistics of operations these complications appeared in a considerable number of cases, but nowadays they are much rarer owing to careful pre-operative treatment, to asepsis, to the development of operative technique and to correct post-operative treatment.

The third table shows the complications of the cataract operations which I performed in the years 1941-1946.

TABLE III

Number of operations	325	
Loss of vitreous	3	= 0.9 %
Expulsive haemorrhage	0	—
Infection	0	—
Haemorrhage into the a.c.	45	= 13.8 %
Prolapse of the iris	4	= 1.2 %
Glaucoma	1	= 0.3 %

Thus loss of vitreous occurred in 3 cases (0·9 per cent.). With one patient who was highly myopic, liquefied vitreous prolapsed from the anterior chamber when the section was made. In another case, also that of a highly myopic patient, the zonular fibres were extremely weak, and in consequence the lens slipped into the vitreous when the capsule was grasped. In both cases the cataract was removed with Weber's loop. In the third case the patient was very nervous, the palpebral fissure was exceptionally narrow and could not be widened by canthotomy. In these three cases I made a complete iridectomy.

I had no case of expulsive haemorrhage or infection. After careful pre-operative treatment these complications do not arise nowadays.

Haemorrhage into the anterior chamber occurred in 45 cases (13·8 per cent.), usually 3-6 days after the operation. The cause was either spontaneous haemorrhage or rupture of the wound. At first I was very perturbed by rupture of the wound when performing operations with a round pupil, but later I saw, to my great surprise, that even in cases when the anterior chamber was entirely filled with blood, no prolapse of the iris occurred. In one case the iris was wedged in the wound; it could be freed from the cicatrix a few weeks later by cyclodialysis. In connection with rupture of the wound the pupil was distorted in four cases (1·2 per cent.).

As the above-mentioned data show, my suture does not prevent rupture of the wound, but it considerably decreases and limits the possibility of the opening of the wound, so that the aqueous of the anterior chamber cannot escape with such force as to carry the iris with it.

Prolapse of the iris or its milder form, wedging of the iris in the wound, may occur a few hours after a cataract operation with round pupil performed with this suture.

Immediately after the operation, or a few hours later, when the edges of the wound are not yet glued together, the iris may slip out of the wound if the eyelids are pressed together. This happened in 4 cases (1·2 per cent.) of my cataract operations. I had this unpleasant surprise when changing the bandage for the first time, 24 hours after the operation. After anaesthesia with pantocain and careful opening of the wound I could replace the iris with a cyclodialysis spatula in two of the cases, but in the other two cases, the lips of the wound were already glued together so firmly that I could only excise the prolapsed part of the iris with forceps and scissors.

On account of this experience I think it would be better to change the bandage for the first time in the afternoon of the day of the operation, because then the wound is not yet firmly closed, and it is easy to replace the prolapsed knuckle of the iris.

Apart from rupture of the wound, distortion of the iris occurred in another 6 cases (1·8 per cent.), probably as a consequence of the eyelids having been strongly pressed together in the hours following the operation, as in the case of prolapse of the iris, or because of inefficient reposition. It is of no importance, and can be considered merely as a minor cosmetic disadvantage.

Secondary glaucoma occurred in 0·3 per cent. After an intracapsular cataract operation with a round pupil a widespread detachment of the choroid occurred, but three weeks later it was attached again. Six weeks after the operation the tension had increased to 60 mm. Hg. Pilocarpine was ineffective, so an iridectomy had to be performed. After this the tension decreased for some time, but six months later it was again 56 mm. Hg, so I decided to perform a cyclodialysis, which permanently reduced the tension. No case of secondary glaucoma occurred in consequence of iris prolapse, impacted iris, or displacement of the pupil, as might have been expected.

Among other less important complications I saw detachment of the choroid in 5 cases, but this always disappeared after a while. I never observed detachment of the retina.

After extra-capsular operations and rupture of the wound a slight irritation of the iris sometimes developed, but with mydriatics and warm compresses it was possible to quieten the eye so that other treatment proved unnecessary.

From all this we can see that the round pupil cataract operations performed with adequate sutures yield much better results than the older " flap method " carried out with a complete iridectomy and

without sutures. The operation with a round pupil is quite free from danger when performed according to my method. I wish to emphasise that this operation may be done even in cases upon which we would not have dared to operate formerly.

This is proved by the fact that among the operations mentioned in my statistics there were 25 cases of patients with impaired hearing, 4 cases of stone-deafness, 6 cases of high myopia, 1 case of advanced Graves' disease, 2 patients suffering from emphysema and severe attacks of dyspnoea, 2 cases of nystagmus—even during the operation—2 cases of deaf and dumb persons, 1 epileptic patient and one with senile tremor of the head. In all these cases I performed successful operations with round pupils, and the state of the patients had not the slightest influence either upon the operation or upon the healing of the wound.

I must mention, however, that operations with a round pupil should be performed by skilful and experienced eye surgeons only. Beginners should practice the flap operation with a complete iridectomy and perform this technically more difficult operation only after considerable experience.

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THE ILLUMINATION OF THE SNELLEN CHART*

BY

M. GILBERT *and* R. G. HOPKINSON

THE problem of adequate lighting in schools, homes, offices and buildings in general has given rise to a study of the effect of illumination and contrast on visual performance. The programme of work has been carried out in close collaboration with Mr. H. C. Weston, of the Medical Research Council, to whom the authors' thanks for the benefit of valuable discussions are due, and under the aegis of the Joint Committee on Lighting and Vision of the Building Research Board and the Medical Research Council.

It was thought that clinicians would be interested in particular in the effect of illumination level on the visual acuity of observers as assessed by the standard Snellen chart.

The subjects of the experiment were 15 adults from the staff of the Building Research Station, in the age group 20-40. They

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TABLE 1—*Classification of Subjects Employed on Visual Acuity Tests*

GROUP 1—*Subjects with Normal Acuity*

Subject	Binocular Acuity on Snellen Chart at 30 f.c. (M.R.C.)	Refraction		
			R.E.	L.E.
1. A.B.	6/4.5	Emmetrope.	—	—
2. C.M.P.	6/4.5	Myope, corrected.	−2.0	−2.75
3. *H.M.	6/4.5	Hypermetrope, corrected.	+4.5, −0.5 ax. 30°	+4.5, −0.5 ax. 130°
4. W.H.W.	6/4.5	Uncorrected.	+0.25, −0.75 ax. 180°	+0.25, −0.75 ax. 160°
5. *M.G.	6/4.5	Myope, corrected.	−3.25, −1.75 ax. 180°	−2.75, −2.5 ax. 180°
6. *C.P.	6/6	Astigmat, corrected	−1.0 ax. 155°	−1.5, ax. 20°
7. *E.S.J.S.	6/6	Hypermetrope, corrected.	+4.0, −0.5 ax. 180°	+3.75, −0.5 ax. 180°
3. *H.M.	6/6	Hypermetrope, uncorrected.	*see* 3	above
8. *P.M.	6/6	Hypermetrope, corrected.	+3.0	+3.0, −1.0 ax. 120°
6. *C.P.	6/7.5	Astigmat, uncorrected.	*see* 6	above

GROUP 2—*Subjects with Moderate Acuity*

9. W.E.S.	6/9	Myope, uncorrected.	−0 75, −0.5 ax. 180°	−0.5
10. G.M.	6/9	Astigmat, uncorrected.	−1.75 ax. 5°	+0.5, −1.75 ax. 175°
5. *M.G.	6/12	Myope, partial correction.	Full cyl. correction, (*see* 5 above) partial sph. correction (−1.0 sph.)	
11. G.B.	6/18	Astigmat, uncorrected.	−2.5 ax. 90°	−2.5 ax. 95°
12. H.My.	6/24	Myope, uncorrected.	−1.75	−2.0
13. *M.L.	6/24	Myope, partial correction (for full correction *see* 13 below).	−2.75, −1.0 ax. 90°	−3.5, −1.25 ax. 95°
14. J.F.	6/36	Hypermetrope, uncorrected.	+1.75, −0.25 ax. 180°	+1.5, −0.5 ax. 65°
15. J.P.	6/36	Myope, uncorrected.	−2.0, −1.0 ax. 180°	−1.0, −1.0 ax. 160°

GROUP 3—*Subjects with Poor Acuity*

8. *P.M.	6/36	Hypermetrope, uncorrected.	*see* 8	above
7. *E.S.J.S.	6/60	Hypermetrope, uncorrected.	*see* 7	above
5. *M G.	6/60	Myope, uncorrected.	*see* 5	above
2. *C.M.P.	6/60	Myope, uncorrected.	*see* 2	above
13. *M.L.	6/60	Myope, uncorrected.	−4.5, −0.75 ax. 120°	−5.5, −0.5 ax. 110°

* Subjects marked thus made observations with and without their correction.

varied from emmetropes of 6/4·5 vision to ametropes of 6/60 vision. Various refractive errors were included in the sample. Some of the observers who habitually wore a correction made observations with and without their correction, and in addition two subjects (both myopes) made observations with a partial correction with which they were familiar. Table I summarises the refractive defects of these observers, which were measured by Mr. J. L. H. Moss, of the Medical Research Council, who also assessed the visual acuity on a Snellen Chart illuminated to 30 ft. candles by fluorescent ("daylight") lamps.

For the observations, the subject sat 6 metres from a white wall on which the Snellen chart was displayed. The whole wall as well as the chart itself was illuminated by screened incandescent light sources. Additional room lighting produced a brightness of the surroundings of the same order as, but lower than, the brightness of the chart.

After an initial period of adaptation, the observer was asked to read the letters on the Snellen chart with an illumination of only 0·1 ft. candles. When he had read as far as possible, the illumination was slowly raised to 3 ft. candles (a change of 30 : 1) and the chart was again read as far as possible. Finally the illumination was raised to 100 ft. candles (a further change of approximately 30 : 1). It was felt that familiarity would not influence the reading of the chart at the higher levels of illumination, since the smaller letters became visible only at these higher levels, and were not recognised at the lower levels. There was in addition a considerable time interval between the successive showings of the chart, so that it was unlikely that the subject would retain any clear memory of the chart, as a number of other charts (with different contrasts, etc.) were also read at each level of illumination. It should also be mentioned that a magnified chart was produced photographically to enable a complete line of letters of the 6/60, 6/36 and 6/24 size to be available for those subjects with poor vision.

The results obtained were plotted in the form of a relationship between illumination (log. scale) on the chart, and line acuity (inverse log. scale of angular subtense of critical detail) for each of the 15 subjects. The subjects were then grouped in accordance with the Snellen acuities measured by the refractionist, and the observations in each group were averaged. The purpose of this grouping was to show whether the effect of illumination on acuity was the same or different for observers with normal or with subnormal vision.

The results are shown on Figs. 1A and 1B. It can be seen from the averaged curves that an increase in illumination of the

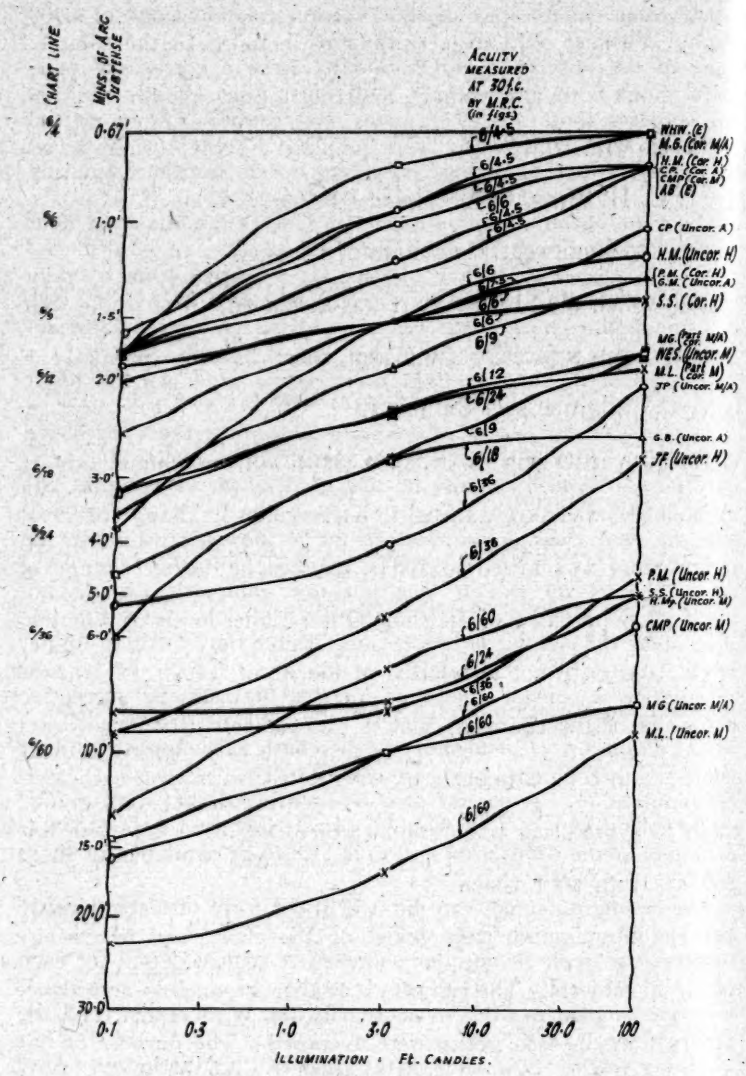

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FIG. 1A. ILLUMINATION *v.* ACUITY FOR STANDARD SNELLEN CHART.

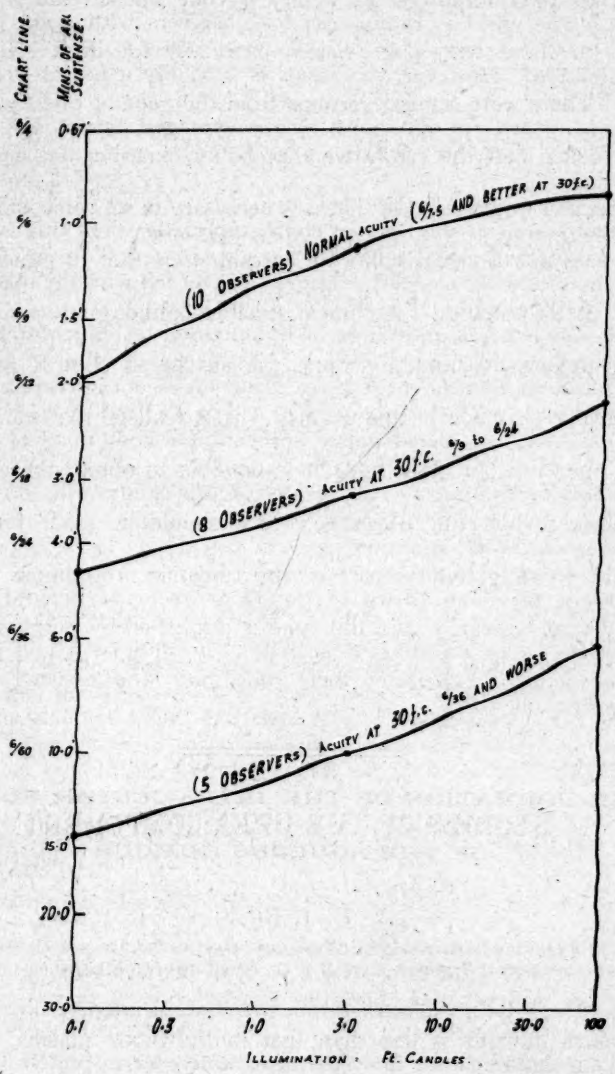

FIG. 1 B. ILLUMINATION v. ACUITY FOR STANDARD SNELLEN CHART.
(AVERAGES FOR OBSERVERS WITH SIMILAR ACUITIES).

order of 10:1 improves the acuity by one line on the Snellen chart. The effect is rather less for observers with good vision than for those with poor vision, especially for high levels of illumination. However, the result is probably a useful working rule. There were some deviations from the general rule by some subjects, which are not shown by the averaged curves, but there is evidence that the errors were probably experimental and not systematic.

The data would suggest that it is necessary to set some standard of illumination of the Snellen chart, especially when this is used as a pass test of visual acuity for entrants to a trade or profession. The investigation was not, of course, concerned with the optimum level of illumination for clinical practice, although it would be of interest to know the range of illumination levels within which clinicians would normally work. A survey of clinical practice was made in 1928 in the U.S.A.,* but no recent surveys appear to have been made in this country. It is realised that for visual examinations conducted under unfavourable conditions of working, the clinician often finds it impossible to obtain the desired standard of lighting. The results of this study will, however, indicate to him the allowance which should be made for such deficiencies in illumination.

The investigation is part of the research programme of the Building Research Board of the Department of Scientific and Industrial Research, and this note is published by permission of the Director of Building Research. The authors would like to acknowledge the help of their colleagues who assisted in the experimental work.

THE FORMATION OF THE INTRA-OCULAR FLUIDS. STUDIES OF THE UREA COMPONENT OF THE AQUEOUS HUMOUR

BY

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It has long been established that the concentration of urea in the aqueous humour is less than that in the blood plasma. After making allowance for the 7 per cent. difference in protein content between aqueous humour and plasma, the ratio of the urea concentrations of these two fluids has been determined by various workers using different chemical methods as follows:—

* R. S. Burnap and E. C. Jackson (1928). *Trans. I.E.S.* (U.S.A.), **23**, 1153.

Species	Method	Mean ratio	Reference
7 oxen ... ... 7 dogs ... .. 2 horses	Urease-hypobromite	0.89 0.82 0.87	Andresen (1921)
Horse (pooled aqueous and "typical" plasma)	Urease	0.94	Duke-Elder (1927)
14 cats	Urease-gasometric	0.75	Adler (1933)
10 dogs, 3 rabbits	Aeration-titration	0.70	Walker (1933)
1 dog, 2 cats 4 rabbits	Conductimetric	0.90	Benham (1937)
21 cats	Aeration Nesslerisation	0.73	Moore, Scheie and Adler (1942)
3 cats	Urease-Nesslerisation	0.77	Scheie, Moore and Adler (1943)
4 rabbits	Aeration-titration	0.66	Kinsey and Grant (1942)
14 rabbits... ...	Urease-diffusion	0.88	Kinsey and Robison (1946)

If the blood-aqueous barrier were a simple semi-permeable membrane and the aqueous humour a dialysate or ultrafiltrate of the blood plasma, non-electrolytes such as urea would be equally partitioned per unit volume of water between the plasma and the aqueous humour. The existence of a urea deficit in the intra-ocular fluids indicates that either the nature of the blood-aqueous barrier or conditions within the eye are such as to modify this equilibrium, by :—

(*a*) selective secretion of urea across the barrier out of the eye (Adler, 1933).

(*b*) utilisation of urea within the eye, or by

(*c*) the existence of a continuous bulk outflow of aqueous humour from the eye so that the rate of drainage of urea from the eye exceeds the rate of entry of this substance into the eye (Kinsey and Grant, 1942.)

In the present paper a kinetic study of the permeability of the blood-aqueous and blood-vitreous barriers to urea has been undertaken, the aqueous/plasma concentration ratio has been re-determined, the mechanism of entry of urea into the eye studied and evidence of utilisation of this substance investigated. Its

mode of exit from the eye will be considered in a subsequent paper.

Part I—Kinetic Studies

The permeability to urea of the blood-aqueous barrier

Experimental

In order to demonstrate that the blood-aqueous barrier is permeable to urea a kinetic study of the transport of this substance from the plasma to the intra-ocular fluids was undertaken.

The principle underlying this type of experiment was to maintain a constant high blood-urea by continuous intravenous injection of an isotonic solution into an animal under pentabarbitone (Nembutal) anaesthesia. The renal vessels were tied to prevent rapid excretion of the substance during the injection. One eye was enucleated immediately before the initial injection to give a value for the initial urea concentration within the eye: a sample of blood was simultaneously taken from the femoral artery. An initial injection of 20 mls. of 6 per cent. urea was then made within one minute to raise the blood urea rapidly to a figure of between 100 and 200 mg./100 ml. H_2O, and further injections were made at intervals to maintain this high blood level since experience had shown that a stable level could be maintained by suitable boosts of urea solution. Samples of blood were removed at 10 minute intervals to check the constancy of this blood level. After a suitable interval (30 or 60 mins.) the other eye was enucleated and the final blood sample taken.

Fluids were removed from the eye as follows: aqueous was withdrawn from the anterior chamber, immediately after enucleation, by means of a clean, dry syringe; the vitreous body was obtained by freezing the enucleated eye in solid CO_2, cutting the frozen eye round the equator, removing the frozen vitreous with forceps, thawing it and forcing it through a glass wool filter to break up its gel structure.

Urea in this and all subsequent experiments was determined by the urease-micro-diffusion method of Conway (1946). This method was found to give consistent and accurate results with fluids of low and of high protein content, full recovery of added urea within 1 per cent. being obtained with plasma, aqueous and vitreous. The correction for plasma proteins was taken as 7 per cent. and all results are calculated as mg. per 100 mls. of water. In all experiments it is assumed that the urea content of the aqueous of a pair of normal eyes is identical; determinations of the urea contents of the aqueous of the two eyes of a pair show that this assumpion is justified within 1 per cent.

Results

Detailed results are presented in Table I. These results have been calculated in terms of the permeability constants for aqueous humour (K_A) and for the vitreous body (K_V) as defined by Davson and Quilliam (1940), where $K = 100 \log \frac{(S - A_1)}{(S - A_2)} \cdot \frac{1}{(t_2 - t_1)}$ (S = mean plasma urea concentration; A_1 = initial aqueous urea concentration at time t_1; A_2 = final aqueous urea concentration at time t_2. Time is expressed in hours.)

The results show that the rate of penetration of urea into the aqueous is consistently higher than that into the vitreous: mean $K_A = 11{\cdot}9$, mean $K_V = 5{\cdot}4$.

TABLE I

KINETIC STUDIES—RATE OF PENETRATION OF UREA INTO THE EYE (CAT)

(*a*) *Penetration into the aqueous humour.*

The permeability constant $K_A = 100 \log \frac{(S - A_1)}{(S - A_2)} \cdot \frac{1}{(t_2 - t_1)}$

(Concentration of urea expressed as mg/100 g H_2O)

Expt.	Blood 1	Blood 2	Aqueous 1	Aqueous 2	Time (mins.)	K_A
10	72.0	124.3	52.0	63.1	33	13.2
12	58.0	94.2	45.6	50.8	32	9.4
13	21.1	68.2	15.8	23.2	30	13.2
15	70.1	169.8	57.0	67.8	30	8.7
16	53.2	154.7	35.0	45.8	30	8.2
17	48.3	85.9	54.2	61.0	30	20.8
21	81.6	149.5	68.9	81.4	30	14.6
23	45.6	114.0	35.1	67.5	122	13.2
27	59.9	214.5	36.3	92.7	123	8.1
28	55.6	131.7	43.5	55.4	33	11.2
29	58.6	171.6	46.3	98.3	123	11.3
30	88.3	180.7	90.4	127.1	120	11 3
31	75.0	135.4	64.7	95.5	122	12.2
					Mean	11.9 ±1.5

(*b*) *Penetration into the vitreous body.*

Permeability constant $K_V = 100 \log \frac{(S - V_1)}{(S - V_2)} \cdot \frac{1}{(t_2 - t_1)}$

(Concentration of urea expressed as mg/100 g H_2O)

Expt.	Blood 1	Blood 2	Vitreous 1	Vitreous 2	$t_2 - t_1$ mins.	K_V
23	91.2	225.6	69.5	113.0	122	7.0
27	59.9	214.5	59.3	83.6	123	3.6
28	55.6	131.7	24.9	29.3	33	3.5
29	58.6	171.6	48.0	73.4	123	4.9
30	88.3	180.7	69.5	94.6	120	5.5
31	75.0	135.4	62.6	85.9	122	8.2
					Mean	5.4±0.6

Part II—Static Studies

(*a*) THE AQUEOUS/PLASMA RATIO

Experimental

Fluids were removed simultaneously from animals under pentabarbitone anaesthesia by the methods already described.

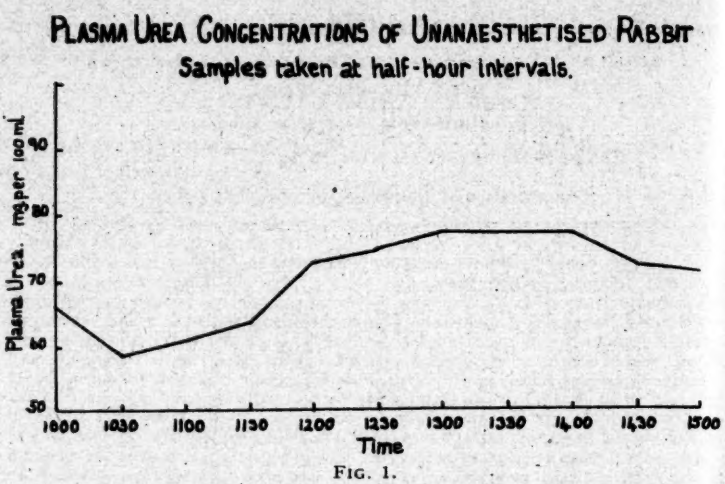

FIG. 1.

A study was also made of the fluctuations of the blood urea level in the unanaesthetised animal by taking blood samples at half-hourly intervals. The results, which are plotted in Fig. 1, show that in the course of 3 hours the urea concentration varied between 59 and 78 mg. per cent., a difference of 24 per cent., which will account for the wide scatter of the experimental ratios since changes of urea concentration in the aqueous will lag behind the changes in the blood.

TABLE II

THE DISTRIBUTION OF UREA BETWEEN BLOOD PLASMA, AQUEOUS HUMOUR AND VITREOUS BODY OF CATS

(Concentration of urea expressed as mg/100 g H_2O)

Expt.	Plasma	Aqueous	Vitreous	Aqueous / Plasma	Vitreous / Plasma
9	57.7	45.7	51.4	0.80	0.89
10	72.0	52.0	44.1	0.72	0.61
12	58.0	45.6	44.9	0.78	0.77
13	21.1	15.8	—	0.75	—
15	70.1	57.0	—	0.81	—
16	53.2	35.0	—	0.66	—
18	32.6	22.6	—	0.69	—
20	30.2	25.4	—	0.84	—
21	81.6	68.9	—	0.84	—
23	45.6	35.1	34.7	0.77	0.76
25	47.1	35.0	34.2	0.76	0.73
27	59.9	36.3	—	0.61	—
28	55.6	43.5	—	0.78	—
29	58.6	46.3	48.0	0.79	0.82
31	75.0	64.7	62.6	0.86	0.83
			Means	0.76±0.013	0.77±0.012

THE DISTRIBUTION OF UREA BETWEEN THE BLOOD PLASMA AND AQUEOUS HUMOUR OF RABBITS

Expt.	Plasma	Aqueous	Aqueous/Plasma
45	40.4	31.0	0.76
47	74.8	59.9	0.80
48	48.7	32.8	0.68
50	54.0	40.5	0.74
51	65.8	52.2	0.79
53	31.0	25.4	0.79
54	48.5	34.0	0.70
55	52.0	37.4	0.72
57	71.9	50.3	0.74
58	66.5	52.5	0.79
		Mean	0.75±0.02

Results

The distribution of urea between aqueous humour, vitreous body and plasma is shown in Table II. The existence of a deficit of urea in the intra-ocular fluids compared with the plasma water is confirmed. The mean aqueous/plasma ratio of 15 cats was found to be 0·76, that of 10 rabbits 0·75; the mean vitreous/plasma ratio of 7 cats was 0·77. Infinity values obtained by maintaining the blood concentration at a high level for many hours showed that apparent equilibrium between the two fluids had been re-established at the end of 3½ hours: this infinity ratio had a mean value of 0·73.

(*b*) THE UTILISATION OF UREA WITHIN THE EYE

Urea is regarded as the end-product of nitrogen catabolism in the mammal, and no evidence has so far been adduced that this substance plays any part in the synthetic processes of the body. The possibility that the difference in the urea concentration of blood and intra-ocular fluids may be due to utilisation within the eye by the metabolic activities of the lens, ciliary body or retina was nevertheless explored by both *in vitro* and *in vivo* experiments.

IN VITRO EXPERIMENTS

Study of the exchange between the lens and its environment was made with lenses excised from the enucleated eyes of rabbits and cats.

Assuming (1) that urea enters the eye by a process of diffusion, secretion, or filtration, not yet fully elucidated, and is removed by drainage, (2) that the urea concentration of the fluid crossing the blood-aqueous barrier is identical with that of plasma, (3) that the drainage rate from the anterior chamber is 4 c.mm. per min. (Kinsey and Grant, 1942; preliminary results of studies in this laboratory indicate that the rate is much higher in the cat), and (4) that the blood urea concentration is 40 mg. per cent., that the aqueous/plasma ratio is 0·75, and (5) that the volume of aqueous humour in the cat is 1·0 ml., then the quantity of urea entering the eye per hour is

$$\left(\frac{40}{100} \times \frac{4}{1{,}000} \times 60 \right) \text{mg.}$$

and the quantity leaving the eye per hour is

$$\left(\frac{30}{100} \times \frac{4}{1{,}000} \times 60 \right) \text{mg.}$$

It follows that the quantity of urea removed per hour from the aqueous humour between its entrance to, and its exit from, the eye will be

$$\frac{(10 \times 4 \times 60)}{10^5} \text{ mg.} = 0{\cdot}024 \text{ mg. per hour.}$$

If the metabolic activity of the lens is the factor responsible for the removal of urea from the aqueous so as to account for an aqueous/plasma ratio of 0·75, then the surviving lens immersed in a physiological medium containing urea should remove urea from this medium at a constant rate of 0·024 mg. per hour.

Experimental

The lens was removed from the excised eye, dried on filter paper and weighed, the whole procedure occupying less than 10 minutes. It was then transferred to a specimen tube containing fresh ox aqueous from eyes obtained from a slaughter-house and kept on ice until used; to this medium at pH 7·4 urea was added to give the required concentration. In the first set of experiments the lenses were incubated for 24 hours at 0°C., in subsequent experiments the incubation time was 2 hours at 37°C.; there is no obvious criterion of viability of a lens, and it was considered probable that the survival time of an isolated lens even in a physiological medium is a matter of a few hours only.

The urea concentration of this ox aqueous medium was fortified by added urea so that samples containing approximately 20, 50 and 80 mg. per cent. were obtained: the 2 ml. quantities employed in each experiment would thus contain 0·4, 1·0 and 1·6 mg. of urea respectively. After incubation for the required time the urea concentration of the medium and of a blank control of the same solution was determined.

TABLE III

EXPERIMENTS ON SURVIVING CAT LENSES INCUBATED FOR A STATED TIME AT A STATED TEMPERATURE IN OX AQUEOUS CONTAINING VARYING UREA CONCENTRATIONS TO SHOW THE QUANTITY OF UREA EXTRACTED FROM OR ADDED TO THE MEDIUM BY THE LENS DURING INCUBATION

(Urea concentrations expressed as mg/100 g H_2O)

Urea conc. of aqueous of eye from which lens was excised	Urea conc. of medium before incubation	Urea conc. of medium after incubation
(i) Incubation for 24 hrs. at 0°C.		
57.0	49.7	44.9
57.0	49.7	51.1
50.3	50.5	53.3
50.3	49.7	52.5
(ii) Incubation for 2 hrs. at 37°C.		
53.6	80.8	62.5
53.6	80.8	59.9
40.1	79.1	47.9
40.1	79.1	49.6
50.0	49.1	50.8
50.0	49.1	53.4
40.1	49.1	51.4
40.1	49.1	56.5
25.1	15.6	18.7
25.1	15.6	19.3
20.3	18.6	25.1
20.3	18.6	24.0

Results

Detailed results are presented in Table III. They show that such differences as exist in the urea concentration of the medium before and after immersion of the lens in it for two hours can be accounted for by diffusion of the substance from a medium with higher, to a medium with lower concentration of urea; thus urea is removed by the lens from the medium when this contains a high concentration of the substance, but is added to the medium when the urea concentration of the medium is below that of the aqueous with which the lens was previously in equilibrium.

IN VIVO EXPERIMENTS

(i) ON THE EXCISED EYE

Experimental

The question of the utilisation of urea by the structures within the eye was further investigated by removing both eyes from the animal (rabbit) within as short a space of time as possible, evacuating the aqueous from one of the pair

immediatelv and determining the urea concentration of this fluid. The fluid of the other eye was evacuated after it had been kept at 37°C. for two hours and its urea concentration determined. Any difference in the urea concentration of the aqueous in the two eyes would indicate utilisation of urea within the eye by such vital processes as continued to function.

TABLE IV

EXPERIMENTS ON THE EXCISED EYE SHOWING THE UREA CONCENTRATION OF THE AQUEOUS HUMOUR OF A PAIR OF EYES, ONE AT THE TIME OF EXCISION AND THE OTHER TWO HOURS AFTER EXCISION. (RABBITS).

(Urea concentration expressed as mg/100 g H_2O)

Urea conc. of aqueous in two eyes of a pair	
(i) at time of excision	(ii) 2 hrs. after excision
65.2	64.0
45.8	44.0
56.5	54.9
44.0	43.5
49.2	48.0

Results

Results are presented in Table IV: these show that the differences in concentration initially and at the end of the two hours are too small to account for a utilisation sufficient to lower the aqueous urea concentration to 25 per cent. below that of blood. The volume of a rabbit's aqueous is about 0·25 ml. so that a difference of 1·2 mg. per cent. represents a loss of only 0·0015 mg. per hour: the theoretical rate to achieve the 25 per cent. deficit is 0·006 mg. per hour.

(ii) EXPERIMENTS ON THE APHAKIC ANIMAL

Experimental

If the lens is the factor responsible for removing urea from the intra-ocular fluids, the aphakic eye will show an aqueous/plasma ratio which approaches unity. The lens of one eye was removed in a series of five rabbits by the standard surgical procedure for extra-capsular extraction. After an interval of six weeks to allow for complete healing, fluids were withdrawn from both eyes simultaneously and a blood sample obtained from the aural vein. Utilisation of urea by the lens would result in a lower concentration of urea in the unoperated eye compared with the aphakic eye.

Results

Results presented in Table V show that the unoperated eye consistently contained a slightly lower urea concentration than did the aphakic eye. The mean aqueous/plasma ratio of the

TABLE V

EXPERIMENTS ON THE APHAKIC EYE. UREA CONCENTRATION OF AQUEOUS HUMOUR IN THE NORMAL AND THE APHAKIC EYE OF A PAIR. (RABBITS).

(Concentration of urea expressed as mg/100 g H_2O)

Plasma	Normal eye	Aqueous / Plasma	Aphakic eye	Aqueous / Plasma
33.3	25.4	0.76	27.7	0.83
71.2	55.3	0.77	57.1	0.80
46.3	36.6	0.79	37.9	0.82
89.8	68.9	0.76	71.2	0.80
61.0	44.5	0.73	47.5	0.78

normal eye is 0·76, that of the aphakic eye is 0·81; although the aqueous/plasma ratio is raised in the aphakic eye it has not become sufficiently close to unity for utilisation of urea by the lens to be the explanation of the urea deficit within the eye.

Part III—The rôle of ultrafiltration in the formation of the intra-ocular fluids

(In collaboration with E. Bárány*)

Kinsey and Grant (1942) conclude from their study of aqueous humour dynamics that electrolytes are secreted across the blood-aqueous barrier but that water and non-electrolytes enter the eye by ultra-filtration. For ultra-filtration to separate a fluid from the blood against the colloid osmotic pressure of the blood (about 25 mm. Hg) and against the intra-ocular pressure (25-30 mm. Hg) a capillary pressure greater than 50-55 mm. Hg would be required; the greater the capillary pressure above this level the greater will be the rate of ultra-filtration. In the absence of any compensatory mechanism stabilising capillary pressure (and observations by Bárány of the capillaries of a rabbit's ear have revealed no such mechanism) any alteration of arterial pressure will materially affect the driving force across the membrane and, therefore, the rate of ultra-filtration. A measure of the part played by ultra-filtration can thus be obtained experimentally by variation of this pressure factor.

Reduction of the local capillary pressure and of the intra-ocular pressure can be produced by carotid ligation. As previously shown by Bárány (1946, 1947*a*) ligation of one common carotid in rabbits causes a fall of blood pressure, as measured in the

* Physiological Institute, University of Uppsala.

central artery of the ear, of the order of 30-40 per cent. and a fall of intra-ocular pressure of 15-20 per cent. on the affected side for a period of at least 24 hours. If ultra-filtration is a significant factor such a fall of blood pressure could be expected to cause a considerable reduction in the rate of aqueous flow and hence in the rate of entry of water into the eye, an effect which should result in a rise in the urea concentration of the aqueous. Unilateral carotid ligation was accordingly performed upon a series of 10 rabbits, and the urea concentrations of the aqueous of the normal and affected eye compared.

Experimental

The common carotid artery was tied on one side in rabbits under pentabarbitone anaesthesia, the van Leersum loop technique being employed. After 24 hours, when the animals had completely recovered, they were killed by decapitation and the aqueous removed from both eyes as quickly as possible. Arterial blood was collected from the neck.

TABLE VI

THE EFFECT OF REDUCING THE ARTERIAL PRESSURE BY CAROTID OCCLUSION UPON THE UREA CONCENTRATION OF THE AQUEOUS HUMOUR OF RABBITS.

(Concentration of urea expressed as mg/100 g H_2O).

Expt.	Side tied	Plasma	Aqueous on untied side	Aqueous on tied side	Difference Tied — Untied	Duplicates agreed within	Ratio Aqueous / Plasma
45	L	80.9	62 1	69.3	+ 7 mg %	2 %	0.76
47	L	74.8	59.9	66.6	+ 7 mg %	2 %	0.80
48	L	48.7	32.8	37.8	+ 5 mg %	3 %	0.68
50	L	54.0	40.5	39.5	— 1 mg %	1 %	0.74
51	L	65.8	52.2	48.0	— 4 mg %	2 %	0.79
53	R	31.9	25.4	26.6	+ 1 mg %	3 %	0.79
55	R	48.5	34.0	30.6	— 3 mg %	1 %	0.70
55	R	52.0	37.4	38.4	+ 1 mg %	2 %	0.72
57	R	71.9	50.3	53.6	+ 3 mg %	2 %	0.74
58	R	66.5	52.5	51.4	— 1 mg %	3 %	0.79
						Mean	0.75 ± 0.02

Results

Results are presented in Table VI. These show that lowering the systemic blood pressure by carotid ligation has no significant influence on the concentration of urea in the aqueous; the ratio of concentrations of aqueous (occluded) to aqueous (control) = 1·028 ± 0·025.

Discussion

The blood-aqueous barrier has been shown by kinetic studies to be permeable to urea although the rate of penetration of this substance into the eye is slower than that of water, of other non-electrolytes such as ethyl alcohol, glucose, or glycerol and corresponds with that of other nitrogenous substances such as creatinine, glycine or alanine. The permeability constants of these substances are compared in Table VII.

This relatively slow rate of penetration is surprising in view of the rapidity with which urea penetrates membranes in other parts of the body, *e.g.*, it penetrates the red cell envelope 35 times faster than does glycerol and yet its apparent rate of entry into the eye is only half that of glycerol. If entry into the eye occurred by

TABLE VII

COMPARISON OF PERMEABILITY CONSTANTS K_A AND K_V.

Substance	K_A	K_V	Species	Reference
Water ...	c. 300	—	Rabbit	Recalculated from Kinsey, Grant and Cogan (1942).
Ethyl alcohol	c. 90	—	Rabbit	Recalculated from Palm (1947).
Glucose ...	34	11	Cat	Davson and Duke-Eider (1948).
Glycerol ...	22	5	Cat	Davson, Duke-Elder, Maurice, Ross and Woodin (in press).
Creatinine ...	14	1.9	Cat	Ibid.
Glycine ...	13.5	1.0	Cat	Ibid.
Alanine ...	12.7	0·8	Cat	Ibid.
Urea	11.9	5.4	Cat	—

ultrafiltration across a semipermeable membrane through large water-filled pores, non-electrolytes should have a permeability constant which is proportional to the square root of their molecular weights (Davson and Danielli, 1943). Davson and Duke-Elder's (1948) studies of the permeability constants of carbohydrates suggest that these substances pass into the eye at rates inversely proportional to their molecular size. The urea molecule is only one-third as large as that of glucose and yet the glucose molecule enters the eye three times as fast as urea, a fact suggesting that in the case of urea some activity other than a process of ultrafiltration

is involved. Paracentesis of aqueous from the anterior chamber temporarily deranges this selective permeability of the barrier so that the urea concentration of the reformed "secondary" aqueous is at first equal to that of the plasma water, slowly falling to normal within the succeeding 24 hours.

The blood-vitreous barrier has been found to be even less permeable to urea than is the blood-aqueous barrier, the respective permeability constants being 5·4 and 11·9.

Re-determination of the aqueous/plasma and vitreous/plasma concentration ratios has confirmed previous observations that a deficit of the order of 20 per cent. exists between the intra-ocular fluids and the plasma water; an aqueous/plasma ratio of 0·76 was found in the cat and of 0·75 in the rabbit: the vitreous/plasma ratio was 0·77 in the cat.

The existence of this deficit in the intra-ocular fluids might indicate that urea was entering the eye by ultrafiltration and was being removed by entering into the metabolism of the lens or other structures within the eye. This possibility has been examined by a comparison of the aqueous/plasma ratios of the normal and the aphakic eye in rabbits, by *in vitro* studies of the lens and also of the excised eye, but no evidence for any utilisation of urea has been found.

The respective contributions of ultrafiltration and secretion to the formation of the aqueous have been studied by a method due to Bárány (1947*b*). If ultrafiltration were an important mechanism in aqueous formation then, following Kinsey and Grant's (1942) hypothesis, reduction in systemic blood pressure by unilateral carotid occlusion would cause a reduction in the rate of ultrafiltration which would show up as a rise in the urea concentration on the affected side. Such a rise cannot be demonstrated experimentally, from which it has been inferred that ultrafiltration plays little part in the formation of the aqueous humour.

These results are in agreement with the findings of Bárány (1947*b*) who found that reduction of blood pressure had no effect upon the rate of entry on Na^{24} into the aqueous. Bárány (1947*c*) later found that lowering the blood pressure likewise had no effect on the osmotic pressure of the aqueous such as would be expected to occur if ultrafiltration were playing a dominant part in aqueous formation.

These results suggest that some mechanism is present at the barrier to regulate the entry of fluid into the eye so as to maintain the aqueous flow constant irrespective of the systemic blood pressure.

The data presented in this paper thus show that the blood-aqueous barrier offers considerable resistance to the entry of urea

into the eye and that its rate of penetration is independent of the systemic blood pressure; the evidence obtained suggests that urea enters the eye by some process other than simple ultra-filtration.

Summary

(1) The urea concentration in the aqueous humour and the vitreous body has been found to be respectively 76 per cent. and 77 per cent. of that of the plasma water.

(2) The rate of penetration of urea into the aqueous and vitreous has been measured and the corresponding permeability constants calculated. These show that penetration into the aqueous is twice as rapid as into the vitreous and indicate that the blood-aqueous and blood-vitreous barriers offer considerable resistance to the passage of urea from the blood to the intra-ocular fluids.

(3) The urea deficit within the eye is not due to utilisation by structures within the eye.

(4) The rate of penetration into the aqueous has been shown to be independent of the systemic blood pressure and the evidence presented suggests that the substance is transferred across the blood-aqueous barrier by a process other than simple ultra-filtration.

I am indebted to Sir Stewart Duke-Elder and Dr. Hugh Davson for their interest and advice.

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OPHTHALMOLOGICAL SOCIETY OF THE UNITED KINGDOM

THE Annual Congress of the Society, which was held from March 31 to April 2 at the Royal Society of Medicine, was attended by 204 members and 91 visitors. Mr. Frank A. Juler presided over this happy gathering, whose success augurs well for the International Congress to be held in London next year. Many distinguished foreign visitors attended, some of them old friends of the Society. From Utrecht came Professor H. J. M. Weve. The Swiss visitors were Professor Marc Amsler, Professor A. Franceschetti, Dr. B. Semadini and Dr. N. Chomé. Dr. E. Hartmann, although paying his first visit to the Congress, was particularly welcome not only by reason of his official position, but also for his own charm. He has succeeded Dr. P. Mérigot de Treigny as Secretary-General of the Société française d'Ophtalmologie. Other welcome visitors from France were Professor G. P. Sourdille of Nantes, Dr. L. Paufique of Lyon and Dr. S. Vallon of Paris. We were also delighted to see Dr. Professor V. Rossi of Pisa, Professor G. B. Bietti of Pavia, Dr. R. Castroviejo of New York, Dr. A. Fritz of Brussels, Dr. A. C. Copper of Leiden, Dr. J. I. Barraquer of Barcelona, Drs. G. Karpe and J. Ollers from Stockholm, Dr. E. Palm of Lund, Dr. A. Mohn of Oslo, Dr. S. J. Braathen of Stavanger, Dr. B. Nyquist of Bergen, and Dr. H. Skydsgaard of Copenhagen. One pleasant surprise was the arrival from Spain of Dr. Arruga junior, on his way to Leeds, where he will be working with Mr. John Foster. A last-moment illness unfortunately prevented Professor M. A. El Kattan Bey, Dean of the Faculty of Medicine at Cairo, from attending the Meetings.

At the opening session the President extended a cordial welcome to ophthalmologists from abroad, and announced that future Bowman lecturers will receive a medal. Although there was not to be a Bowman lecture this year, medals had already been cast for presentation to former recipients of this honour, and he was glad that three of them were able to receive their medals in person. Sir John Parsons, F.R.S., whose Bowman lecture on the Foundations of Vision was delivered in 1924, stepped forward to receive the token, and was followed by Professor H. J. M. Weve (1939) and Professor Marc Amsler (1948). The President then announced that medals would be despatched to the other living Bowman lecturers — namely, Sir Arthur Keith (1930), Professor van der Hoeve (1932) and Dr. Arnold Knapp (1946).

The subjects considered by Mr. Juler in his Presidential Address were Some Points in the Operation for Acute Glaucoma and some Reflections on Refraction. Corneal Grafting had been chosen as

the content of the main discussion, and the Honorary Secretaries succeeded in assembling a galaxy of world-famous keratoplasticians. Professor Franceschetti, who opened the discussion, was followed by Mr. Tudor Thomas. Professor Sourdille, Dr. Paufique, Dr. Castroviejo, Dr. Barraquer, Dr. Fritz and Professor Bietti all produced interesting observations, and the other openers among British ophthalmologists were Mr. B. W. Rycroft and Mr. D. P. Choyce. Several most illuminating films were shown, and admiration was expressed for Dr. Castroviejo's astonishingly clear colour-photographs. This year the Society was particularly fortunate in the contributions made by people outside its speciality, because Dr. S. P. Meadows and Dr. Macdonald Critchley both read fascinating papers on neuro-ophthalmology, and Mr. D. N. Matthews gave a masterly, richly illustrated survey on the Technique of Plastic Operations in the Neighbourhood of the Orbit.

Abstracts of the above-mentioned and of additional papers will be published in *Ophthalmic Literature*. No clinical meeting was held, because the numbers attending Ophthalmological Society of the United Kingdom Congresses are now too large to permit examination by more than a minority of the members. The substitute plan of arranging a series of illustrated case-descriptions was voted a great success. Dr. Spence Meighan occupied the chair for the President on this occasion.

Professor Franceschetti proposed the toast of the Society after the Annual Dinner held at Grosvenor House on March 31. He reminded us of the close ties of friendship which have linked and still link British with Swiss ophthalmology. In replying to this toast the President referred in terms of warm appreciation to the kindness shown by Professor Franceschetti and by other hosts in Switzerland, France and Holland towards the parties of British ophthalmologists visiting foreign clinics under the auspices of the Faculty of Ophthalmologists. The official guests at the Dinner included Lord Webb-Johnson (President of the Royal College of Surgeons), Sir Henry Dale, F.R.S. (President of the Royal Society of Medicine), Dr. C. Thackray Parsons (Deputy Master of the Society of Apothecaries), Sir Stewart Duke-Elder (President of the Faculty of Ophthalmologists), Mr. F. A. Williamson-Noble (Master of the Oxford Ophthalmological Congress), Mr. D. N. Matthews, Dr. Macdonald Critchley and some of the above-mentioned foreign guests accompanied by their wives. Lord Webb-Johnson and Dr. Macdonald Critchley replied to the toast of the Guests, which had been proposed by Mr. J. H. Doggart. The President's health was proposed in terms of affectionate respect by one of his former house-surgeons at St. Mary's—Miss Ida Mann.

On April 1, a number of the foreign ophthalmologists and their wives were entertained to dinner by the Council of the Faculty of

Ophthalmologists at Apothecaries Hall, where they were received by the President of the Faculty and Lady Duke-Elder. After dinner Sir Stewart Duke-Elder's words of welcome were followed by a short survey of old customs and institutions in the City of London, given by Mr, Frank Law, the Honorary Secretary of the Faculty.

It was felt on all sides that this 1949 Congress went well. Certainly the President communicated a spirit of quiet enjoyment and welcome, and the arrangements made by the Honorary Secretaries and by the Secretariat at 45, Lincoln's Inn Fields made for smooth working of the social occasions as well as the scientific programme. Sincere gratitude has also been expressed to Lord Webb-Johnson, whose invitation to distinguished ophthalmologists from abroad to lecture at the Royal College of Surgeons served two important purposes. We were thereby encouraged to prolong the delights of the Congress, and we were permitted to hear four stimulating talks by Professor Weve, Professor Franceschetti, Dr. Hartmann and Professor Bietti.

FACULTY OF OPHTHALMOLOGISTS

The following is the Honorary Secretary's summary of the business conducted at the last Council meeting on February 18:—

It was learnt that the proposed enquiry into the working of the Supplementary Ophthalmic Service had been postponed. It was reported that following a meeting of the Ophthalmic Negotiating Committee the Ministry had decided to reduce the fee from £1 11s. 6d. to £1 5s. as from April 1 next, and that the turnover should be in the neighbourhood of 5 patients in two hours. The Minister proposed to discuss further with the profession the question of an investigation into the average time taken, and an undertaking had been given that the reduced fee should be suitably adjusted if its reduction was found to be unjustified. The matter was discussed at length and it was decided that the Negotiating Committee should be urged to protest against the reduction, and that each individual member of the Faculty should receive a copy of the Minister's letter with a letter explaining the position.

Mr. Duthie and Mr. Greeves have been elected members of the Standing Ophthalmic Advisory Committee for the National Health Service.

It was decided to send a circular letter to the Senior Administrative Medical Officers of Regional Hospital Boards urging them to set up Ophthalmic Advisory Committees if they had not already

done so, and giving an outline of the constitution of such a Committee. It was further arranged that representatives of the Faculty should call upon the Senior Administrative Medical Officers of Regional Hospital Boards and explain any points which needed explanation.

There were many points in the memorandum from the Joint Emergency Committee (Optical Profession) on the Ministry of Health directive, HMC(48)63, BG(48)66, to which the Council took exception, notably those arising out of the assumption that the report of the joint Sub-Committee of the Faculty and the Joint Emergency Committee represented the views of the Faculty, when in point of fact the Council had repudiated the report. The Honorary Secretary was instructed to write to this effect to the Senior Administrative Medical Officers of the Regional Hospital Boards and to Mr. Giles, Secretary of the Joint Emergency Committee (Optical Profession), and to inform the Ministry that he had done so.

After discussion and some dissent the Council by a majority decision endorsed the suggestion which had been made by the Ministry that the advisability of registration of opticians need not be discussed seeing that the Ministry were prepared to alter the constitution of the Committee to discuss the remaining quesion, *viz.*, the conditions of registration.

Mr. Davenport reported that he had received a copy of the amended memorandum on the training and examination of future entrants to the optical profession, together with a letter from Mr. Giles asking if it would be possible for opticians to attend hospitals during the final year of their training. It was agreed that this latter question could not be discussed until the recommendations of the Joint Advisory Board concerning the training and examination of opticians had been agreed. This memorandum had not been submitted officially to the Faculty.

In reply to a letter the Council suggested that the initiation of the Final Service would best be accomplished in the early phases by consultation with the Senior Administrative Medical Officer and the Ophthalmic Advisory Committee of the area concerned.

A letter was received from the British Medical Association, pointing out that the term of office of the members of the Ophthalmic Services Committees expired on March 31 and suggesting that the present members should be re-appointed. This was agreed.

The Council felt that no action could be taken in the matter of priority prescriptions for glasses in view of the fact that the machines in the country were already working to capacity.

The report was received of the Committee which had sat to consider the question of the examination of cases of miners'

nystagmus and heat cataract under the Workmen's Compensation Act. Mr. Healy explained the report, which was approved and filed with the documents.

Mr. Law reported that the Ministry was interested in the question of corneal graft donors and would be glad to meet representative members to discuss the situation. The following were appointed: Mr. R. C. Davenport, Mr. J. H. Doggart and Mr. A. Lister.

Letters were received from three members regarding alteration of the areas of the regions represented on the Council. The Council agreed that the present regions were unsatisfactory, and it was decided to consider the matter in detail at the next meeting.

NOTES

Gold Medal for the Prevention of Blindness

NEW YORK, March 23:—The Leslie Dana Gold Medal for 1948, a National award given annually for outstanding achievement in the prevention of blindness and the conservation of vision, was presented on March 25, at a dinner in St. Louis to Dr. Lawrence T. Post, Professor of Clinical Ophthalmology and head of the Department of Ophthalmology at Washington University Medical School.

* * * *

University of Glasgow Department of Ophthalmology. *Whitsun Term.* 1949

DURING May a series of meetings will be held in the Department on Wednesdays at 8 p.m. The general arrangements will be similar to the series held last year. A discussion will follow the main paper.

May 4, Prof. W. J. B. Riddell—"European Vacation"; May 11, Dr. Fergus Campbell—"Pupillary Movements"; May 18, Dr. Antoinette Pirie—"The structure of the Vitreous Humour"; May 25, Dr. W. O. G. Taylor—"Bleeding and Clotting within the Eye."

Papers submitted for publication should be sent to:—
The Secretary of the Editorial Committee,
British Journal of Ophthalmology,
Institute of Ophthalmology, Judd Street, London, W.C.1

Such papers should be typewritten in double spacing on one side of the paper only, leaving a 1½ inch margin. The Author's name and address should be plainly indicated. References to the literature should be set out in accordance with the Harvard System, *e.g.*, Langley, J. N. (1919).—*J. Physiol.*, 53, 120. Illustrations should not be fixed to the typescript. They should be numbered in sequence, and the top of each should be clearly marked.

Publication of a paper does not imply that the Editorial Committee agrees with the views expressed therein. The Committee reserves the right to delete redundant words, to modify ambiguous phrases, and to translate foreign idioms into current English expressions. Twenty-five reprinted copies will be sent to the Author (or Authors) of each article free of charge. A form of application will be attached to the Author's galley proofs for any additional copies which the Author may wish to buy.